THE AMERICAN JOURNAL OF ROENTGENOLOGY
RADIUM THERAPY AND NUCLEAR MEDICINE

VOL. 75 MARCH, 1956 No. 3

PRESIDENT'S ADDRESS*

By JOHN E. WIRTH, M.D.

MEMBERS of the Society and Guests: I should like to ask the guests to excuse me a moment while I take this opportunity to express my appreciation to the members for electing me President of their Society. The task seemed staggering at times, but I realize fully that most of the time and effort spent has been more beneficial to me than to the Society. I am grateful for the opportunity you have given me. I thank you!

We are particularly fortunate at this meeting to have, not only a goodly representation of our own Society and regular guests, but also the pleasure of seeing many of our South American colleagues. The Fifth Inter-American Congress of Radiology will be held here immediately after this meeting. Many of our friends from Latin America and Canada have arrived early to attend both meetings. We of the American Radium Society are extremely pleased to welcome these guests to our meeting and sincerely hope they will enjoy and derive as much benefit from the meeting as I know we shall derive from becoming better acquainted with them. Too often peoples of various countries are known to each other only by name. This meeting should afford an excellent opportunity for the names to be coupled with faces and personalities. Welcome!

In the realm of medical societies, the American Radium Society is relatively new and is also relatively small. Despite this, it has had many problems with which it has had to cope. It has survived these problems exceedingly well. Its membership is made up of representatives of diverse medical fields, and it may be because of this diversification that conflicting opinions and theories have been distilled to an essence acceptable to all. The Society has been one of the most progressive of the radiological societies. Its membership of diagnostic and therapeutic radiologists, gynecologists, surgeons, physicists, experimentalists, and even combinations of these, seem bound together by such a cohesive force that they mingle in close friendship despite such a wide variety of ideas and thoughts. May it never become provincial!

The practice of radiology today may, in many ways, be compared with aeronautics. Both fields are in a transitional stage. Not many years ago, some of the earlier, better flyers were referred to as "flying by the seats of their pants." The more adept, and/or luckier ones, took off, flew, and landed successfully. The others were lost

* Delivered at the Thirty-seventh Annual Meeting, American Radium Society, Washington, D.C., April 21–23, 1955.

by the waysides or on mountainsides.

The seemingly gradual, but in reality, rapid development of instrumentation led to many changes in the field. Some of the older flyers adapted themselves easily to the use of these instruments. Others, unable to cope with the new gadgets, were lost in flight or licensed out of their profession. The younger men graduated after intensive training with the newer methods and instruments and even helped to develop newer instruments during their training period. These new men were given basic training in radio range, tower to plane radio, radar—both ground and airborne. Ground controlled approach (G.C.A.) and airborne instrument landing system (I.L.S.) have become commonplace. To prevent spinning out of an overcast other instruments were developed. The rate of turn indicator using the gyroscope came into being as did an air speed indicator and an altimeter. Thus, these younger men developed with an industry that reputedly has made flying one of the safest methods of travel.

Many of these men have become so proficient with all the new instruments that flying becomes almost second nature to them and more time and thought can go into the over-all problem of flying, and not so much time has to be spent on fighting each of the gadgets. One of the most difficult problems is for the young man to trust his instruments rather than rely on his impressions. It is a better gamble that the pilot is off rather than the indicator; as when a pilot, feeling that the plane is tilted, "leans" to compensate for it despite the instruments indicating that he is in level flight.

In similar fashion, many of the earlier radiologists may be said to have practiced "by the seats of their pants." Many of them were extremely good radiologists, as time has proven.

There have been amazing developments in radiological instruments in the last few years. I need not enumerate them to you. Many physicists have come into the picture and have played a large part in developing precise instruments, in helping the physician use them, and in calculating precise radiation dosages prior to their actual administration. Accurate dosage can be calculated in advance of administration in order to give maximum beneficial results with the least unwanted or untoward reactions and complications. In fact, precise measuring and calculating is carried to such extreme in some instances that the preciseness of the measurement used may be out of all proportion to the accuracy of clinical interpretation of the extent of disease. The older physician, brought up on trial and error methods, may recognize these discrepancies; but in the long run, the younger man, with thorough basic training, including some actual practice, can develop and far exceed the proficiency of the former.

The younger man not only has the advantage of good instrumentation, but has available to him the records accumulated by the older man (provided these records are worth more than the match it would take to burn them). He has also the invaluable advantage of survival statistics to indicate which of the older methods has been most successful. (Again, this may be true if adequate records have been kept. Good record keeping is not a happenstance. It is trite to say that a record is no better than the information recorded. Why accurate recording of information is so difficult for so many is not obvious. The busy physician may feel it easier and quicker to carry data in his head. Most realize what a futile practice this is, but do little to overcome it.)

It may be surmised from the above that I feel that there has not been a more propitious time for the young physician to start practice. In contrast to some prior thinking that everything has been learned, there are many fields open, new avenues to be explored, and new methods to be developed. The young man starting out in practice must explore the many avenues left open

by the older physician and radiologist which culminate in the final problem of the etiology and cure of disease.

Who among us is not aware of the multitude of problems each set out to solve in his younger days only to realize that many answers have not been forthcoming despite the vast progress that has been made? Diagnosis and therapy of benign breast lesions is almost as unsatisfactory today as it was twenty-five years ago, probably because mortality figures are negligible but morbidity represents a real problem. Tremendous strides have been made in the identification and therapeutic use of hormones, but these advances seem only to point out more unknown factors. So much is wanting in the understanding and treatment of lymphomas and melanomas that most men have little time to think of the unsolved problems concerning the rarer conditions of fibrous dysplasia of bone and ameloblastomas. The changing concepts of the cause of oral cancer are a good example of the trial and error methods which we go through to obtain dribbles of true information. Syphilis, avitaminosis, abnormal salivary conditions, and more recently, achlorhydria, have each been considered the major cause, and yet ultimately, each may prove to play only a small part in the over-all picture of oral cancer. Some of the newer drugs which have been fairly well proved to have no real value as a cure for cancer may yet cause so many changes in the clinical features of a cancer as to make it hardly recognizable. Hydrocortone ointment which is being applied promiscuously by so many persons to skin lesions may be placed on a superficial skin cancer and so change its clinical characteristics that it cannot be recognized by a good diagnostician. These are only a few of the many avenues for the young man to explore. Unfortunately, in the same way that this young man has much to work with, he has much that he must guard against.

There are many pitfalls for the enthusiastic young man out to solve these many problems. In his constant effort toward the solution of many of the cancer and radiation problems, the younger man must not allow himself to fall into a state where the *products* of his enthusiasm may be difficult to distinguish from quackery.

If the young man were to listen to some quarters regarding the problem of etiology and cure, he might be led to believe that the answer could be obtained by the expenditure of large sums of money. These same quarters mistakenly compare the development of the atom bomb with the finding of this etiology and cure. It is much more probable that the basic knowledge regarding cancer is much more incomplete now than was the basic knowledge in physics immediately prior to the development of the atom bomb.

Probably no more fruitful is the approach of the jack of all trades. Merely because such a man is conversant in so many fields of progress and new developments does not necessarily mean that he will be in a position to choose the correct combination of facts to give the final answer. It is also possible for the younger man to become overwhelmed by the tremendous strides that have been made in all branches of research during the last few years. We must remember that there are ample tasks awaiting those capable of doing good work. A superficial glance at the recent issues of some of the pure research journals is apt to discourage the novice. Work already completed and the numerous and varied fields that are already being investigated by so many, may lead one to wonder what new alleys have not been tried. Unfortunately, the novice may not be aware, in his maze, that there may be no reward at the end of a blind alley. These frustrations should not divert the good man to such an extent that he feels, for the sake of security, that he must work only in vast organizations where his efforts may become a small cog in a vast wheel. As a cog in this vast wheel he might be stimulated to produce for production sake. *The value of such production* must

be determined. There is a tendency now to believe that research has become so complicated that something can be accomplished only in large groups. This belief exists despite the fact that the majority of better basic original findings has been produced by lone individuals. I do not mean to deprecate the fine work and excellent progress being made by the staffs of many of the large institutions of today, but to reemphasize that this is not necessarily the only way findings may be obtained. Further, in this modern world, the good man may be led astray by the monetary returns he can receive by less effort in other fields. In terms of gain in worldly goods, research can hardly compete with labor or industry. We hope that the gain of the research man is a more permanent one. Unfortunately, this is apt to discourage too many who might make excellent contributions to medical progress. In the same way, however, it may be fortunate that the choice is open to all to remain in a confined field with little worldly gain, to go over to the other extreme where there is little more than monetary gain, or to choose the more difficult middle path in which both extremes are combined.

In the broad sense of the word, radiology has played and undoubtedly will play a large part in the solution of the problem of the etiology and cure of cancer. The radiologists and physicists find themselves only a small part of the group handling radioactive isotopes these days. Even the internists have turned to this field in their gropings for answers. From the standpoint of protection of the individual from radioactive materials, this may not be good, but from the standpoint of progress in the medical sciences, it may be an excellent turn of events. It is doubtful that a single etiology and cure will ever be found for the scrap basket term "cancer." But rather it is likely that numerous etiologic factors will be found for the many forms of the disease which are now lumped under this heading. Thus, while trying to find some of the answers to the cancer problem, many basic research problems will be answered by the variety of disciplines involved. Perhaps only out of a variety of approaches will some of the answers be found. I sincerely hope that this scientific meeting will prove to be one step in many directed towards these answers.

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Vol. 75, No. 3

THE BACKGROUND OF RADIUM THERAPY IN THE UNITED STATES, 1906–1956

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IN 1906, the existence of radioactivity had been known for ten years; radium had been discovered in 1898 and its biological effects demonstrated soon after. It had been used in France in superficial therapy and in intracavitary gynecological applications, and in the United States by Dr. Robert Abbe for direct implantation into tumors. In Paris in 1906, the Biological Laboratory of Radium was founded by Wickham and Degrais, with Dominici in charge of the clinical work. About the same time in England the Radium Institute of London was formed. In both these groups chemists, physicists, and members of various medical specialties worked in close cooperation not only in the laboratory but in the treatment of patients. As a result, many of the basic facts of radium physics were early discovered and put to practical use. Among these were the value of filtration and of distance from the source to the involved tissue, and the use of cross-fire. Radon, then called radium emanation, had been discovered and apparatus developed for removing it from the parent radium and dispensing it in aqueous or alcohol solution.

Until 1911 there was no satisfactory method of standardization of radium. In that year, at the request of an international commission, Madame Curie undertook to prepare an accurate standard of a carefully weighed quantity of a pure radium salt. This was deposited in the International Bureau of Weights and Measures, at Sèvres, near Paris, and all other standards in all other countries have been established by comparison with this.

At that time, the only place radium could be obtained was in France or Austria. In fact, Austria had essentially a government monopoly in the Bureau of Mines. A few physicians in the United States had succeeded in obtaining small quantities, frequently not very pure nor well calibrated. They used it empirically, often by methods that would now be considered extremely poor, and yet their results were good enough to warrant enthusiasm.

One of these was Dr. Howard Kelly, professor of gynecology at Johns Hopkins Medical School and the real father of radium therapy in the United States. In 1908 he had obtained a small glass tube containing a few milligrams of radium, and had used it in a number of cases. The following year Dr. Wickham visited this country and aroused in Dr. Kelly and his associate, Dr. Curtis Burnham, a desire to obtain an adequate supply of the material and set up a real clinical program. In 1911 they acquired 130 mg., of which a small amount was in a varnish applicator, 30 mg. in an apparatus for emanation extraction, and nearly 100 mg. in metal tubes. The tubes were used mainly in gynecological treatments, the emanation, in solution, in the treatment of arthritis and gout. (This latter, however, was discontinued after three years.) A year later they received another 200 mg., and by this time convinced of its value, made a contract with the Austrian government for one gram to be delivered in 1913,—by far the largest single order ever placed up to that time. This contract was never fulfilled, because of the rapidly increasing demand by German and Austrian clinics, which absorbed the Austrian supply.

However about this time radium was discovered in Colorado carnotite. In 1911 the Standard Chemical Company was formed by Mr. Joseph Flannery of Pittsburgh to separate radium from this ore. To his chief chemist, Dr. Charles Viol, is due

in great measure the success of this venture. It was a completely new industry, and it was not possible to get any trained radium workers from Europe, so the whole procedure had to be developed from the beginning. The Colorado ore was much poorer than the Austrian pitchblende. Whereas the latter had a gram of radium in 4 or 5 tons, in the former 400 or 500 tons were necessary, and each of these tons had to be handpicked out of a much larger mass of dirt and rock. This was done at the mines, and the crude ore sent to Pittsburgh for refinement. For reducing and purifying one gram of radium from 500 tons of ore, it was necessary to use 10,000 tons of distilled water, 1,000 tons of coal, and 500 tons of chemicals. This gram of radium sold for $120,000. The first radium produced by this company was put on the market in 1913, just as Dr. Kelly found himself refused the purchase of what he wanted in Austria. He was able within a year to obtain 750 mg. from the American company.

Early in 1912 the newly organized Bureau of Mines, of the Department of the Interior of the United States Government, became interested in the best means of exploiting the Colorado radium. After initial plans had been discarded, a cooperative project was set up whereby the Bureau of Mines was to furnish the technical staff, while necessary funds for operating were to be sought from private sources. The radium produced was to be made available for clinical work in selected institutions, depending on the interests of the financial supporters. Dr. Kelly was a moving spirit in the development; he was strongly supported by Dr. James Douglas, a distinguished mining engineer. His interest arose at least in part from the fact that he was a friend and patient of Dr. James Ewing, of the Memorial Hospital in New York. Dr. Ewing had become interested in the clinical possibilities of radium, and was enthusiastic about the hospital's acquiring some.

Accordingly the National Radium Institute was organized in 1913; its technical operations lasted from 1914 to 1917. During this time 8.5 grams of radium were produced, most of which were divided between the Kelly and Memorial Hospitals.

In each of these institutions most of the radium was put into an "emanation plant." It had been found that the radium emanation, or radon, gave off the same rays as the radium itself. (It is now known that the penetrating beta and gamma rays from radium or radon sources are not due to either of these elements, but to their decay products, Radium B and Radium C, which remain in the containers with their parents.) The radon was, however, short-lived, decaying with a half period of 3.85 days, whereas the radium remained practically constant in strength for many years. However each day a new supply of radon could be drawn off, to compensate for what had decayed. Thus the precious radium could be kept in a safe, with no danger of loss, theft, or breakage, while adequate activity could always be available in the form of radon.

The apparatus used by Kelly employed liquid air to freeze the radon and so separate it from other gases. About 1914, Professor William Duane of the physics department of Harvard University devised a chemical method for the purification. His apparatus was installed at the Huntington Hospital in Boston, and the Memorial Hospital, and later, with improvements due to Dr. G. Failla, physicist at the Memorial Hospital, in a considerable number of other institutions. Among these were at least two commercial laboratories set up to sell radon to doctors who did not have their own supply of radium.

During the period prior to the First World War more and more physicians acquired some radium and began to develop methods of treatment. As early as 1914, Dr. William Newcomet's book, *Radium and Radiotherapy*, set forth an impressive list of diseases treated with favorable results. Other publications appeared, and

papers began to be presented before the American Medical Association and other medical organizations.

In October of 1916 a group of about 24 physicians met in Philadelphia and organized the American Radium Society. Their first slate of officers was: President—W. H. B. Aikens, Toronto; Vice President— Russell H. Boggs, Pittsburgh; Recording Secretary and Treasurer—R. E. Loucks, Detroit; and Corresponding Secretary—H. K. Pancoast, Philadelphia. As far as can be ascertained the only charter members still living are Dr. James T. Case, of Santa Barbara, and Dr. D. T. Quigley, of Omaha. The object of the Society, as defined in the constitution soon adopted, and never altered, is "to promote the scientific study of Radium and other sources of ionizing radiation in relation to their physical properties and their therapeutic application."

In the forty years since its organization, the Society has retained this objective, in spite of efforts to divert it to purely a cancer society, or to absorb it into other organizations. Its membership has been kept small; it now numbers about 300. For some time active membership was restricted to physicians; physicists interested in the field could be accepted as associate members. However in 1951 the Society took the progressive attitude that full membership should be open to qualified scientists from other fields, particularly physics, and there are now some 15 such non-medical members.

In 1922 the AMERICAN JOURNAL OF ROENTGENOLOGY became the official journal of the Society, its name being changed to AMERICAN JOURNAL OF ROENTGENOLOGY AND RADIUM THERAPY with the issue of January, 1923.

Initially the Society held its meeting just before the annual convention of the American Medical Association and in the same city. By 1940 there was considerable dissatisfaction with this arrangement. During the war years medical meetings were largely discontinued; when the Radium Society again held scientific sessions, a change of policy was discussed, and it was finally decided to try independent meetings. The first of these, held in St. Louis in April, 1953, was such a success that there has never been any thought of returning to the old arrangement.

To regress to an earlier period, following the organization of the American Radium Society, with its scientific programs furnishing a place for the exchange of ideas, and with the acquisition of a journal for the publication of clinical and experimental results, development and improvement in the clinical use of radium were assured. This development has always been the result of cooperation by physicians and physicists. In the very beginning the doctors in Paris had the aid of Madame Curie and of Becquerel, and those in England of Rutherford, Soddy, and many others. In the United States the association of Duane, and later of Failla and his group at the Memorial Hospital, of Weatherwax at Philadelphia General Hospital, Glasser at Cleveland Clinic, and Stenstrom at the State Institute in Buffalo, have been outstanding. The long list of clinical men working in the development at these institutions would include Janeway, Barringer, Bailey, Quick, Stone and many others at Memorial Hospital, Leddy and Widmann at the Philadelphia General Hospital, Portmann at the Cleveland Clinic, and Gaylord and Schreiner in the State Institute of of Buffalo, but this listing is only the beginning. Then there are the men like Pancoast, Pfahler, Clark, Bowing, Withers, Grier, Ernst, and many others; there is no way of properly distributing credit, and it would be a mistake to try. For every name listed, three others come to mind; one would end with a roll-call of radiation therapists.

The history of radium therapy may be followed through two quite distinct branches, external irradiation and intracavitary or interstitial use. In the early pe-

riod, when only small amounts of radium were available, and little was known of the importance of distance and filtration, small plaques or little bundles of tubes were placed on or quite close to the skin, with the hope of influencing fairly deep tissues. At the same time, any skin change was considered undesirable. "Give my patient a good dose of radiation but don't damage the skin" was an instruction frequently given to the radium therapist. However it was soon realized that this could not be done except for very superficial lesions unless large quantities of radium, well filtered, could be employed. Nevertheless, until the middle 1930's, the gamma rays of radium were so much more penetrating than any x-rays available for therapy that they appeared to offer a real advantage in certain radioresistant growths, if large enough sources could be made available. After the First World War new and richer radium ores had been discovered in various parts of the world, and several institutions acquired relatively large amounts, of the order of from 2 to 10 grams, which they used in large "packs" or "bombs" at several centimeters distance from the skin.

This "telecurie therapy" found enthusiastic advocates in France, Belgium, Sweden, and England, and to a less extent in America. Memorial Hospital, Bellevue Hospital in New York, the Oncological Hospital in Philadelphia, the Chicago Tumor Clinic, were among the groups using this method for a longer or shorter period. Even with large amounts of radium, treatments had to be very long, and depth doses were not very good because radium-skin distances were only of the order of 4 to 12 cm. With the development of x-ray machines operating at one or more million volts, the advantages of telecurie therapy ceased to exist, and most of the large units in this country were broken up. However Dr. Douglas Quick, at the Roosevelt Hospital in New York, using 50 grams of radium in a special type of multi-source unit devised by Dr. Failla, is accumulating an impressive series of cases. Now, with the availability of artificially radioactive cobalt, emitting radiation very similar to that of radium, sources are available which are the equivalent of hundreds of grams of radium, and there is a new surge of interest in this type of therapy.

From early years it was evident that the unique advantage of radium was in intracavitary and interstitial applications. Here the radiations did not first have to traverse normal tissue; the short distance and rapid fall-off of intensity were frequently assets instead of liabilities.

At first containers were rather bulky. While they could be used intracavitarily in gynecological cases, they did not lend themselves to direct implantation in the tumor. In 1914 Stevenson and Joly developed a method of collecting radon in fine glass tubes which they then placed in hollow metal needles. These were inserted directly into the tumor to be treated, and withdrawn at the end of the exposure. Since radon was available only in a few places, this procedure was not employed extensively, but it did give the needed impetus to the production of "radium needles," in which the radium, in the form of pure radium sulfate, was tightly packed into hollow needles of steel or platinum. Dominici, in Paris, had already utilized metal tubes to hold his glass tubes of radium salts; omission of the glass and consequent diminution in size of the container was an obvious step. These needles of small radium content early became popular in Europe, especially in England.

In the United States the Dominici tubes were widely used in gynecological applications, but for interstitial treatments "radon seeds" were used in all institutions having radon plants, and in many others when seeds could be obtained from commercial suppliers. The procedure was first suggested by Prof. Duane about 1915. The radon gas was collected in a very fine capillary glass tube, which was then divided into pieces 3 or 4 mm. long. These could be implanted directly into the tumor by means of a small trocar, and allowed to

remain permanently *in situ*. The radon, decaying at the rate of about 16 per cent per day of the amount present, was effectively gone before the end of a month; the glass, being inert, could be left in place indefinitely. The advantages suggested by Duane were utilization of the beta rays irradiation of the tumor at a slow rate over a considerable period of time, and reduction of trauma.

Dr. Henry H. Janeway, at the Memorial Hospital, worked out practical techniques for use of these sources, and became enthusiastic about them, particularly for lesions about the mouth. However, the treatments often resulted in severe pain for a considerable time, due to the intense necrosis produced around each seed by the readily absorbed beta rays. Since it became evident that, contrary to Duane's ideas, the therapeutic benefit was due to the gamma rays, it appeared that some method of filtering out the beta rays was necessary. This was achieved in the small platinum needles used in France and England, but these had the disadvantage of having to be sutured into the tissue and later removed.

An ingenious suggestion was made by Dr. Arthur Heublein, of Hartford, that each glass seed should be injected with a small quantity of bismuth paste surrounding it, and he developed a special needle for the purpose. The method was not successful, due mainly to the difficulty in really surrounding the seed with the paste.

Dr. Failla then set about developing a filtered seed. After trying various schemes including the use of lead glass, he hit upon the idea of using pure gold capillary tubing. This was very soft, and was self-sealing when cut with rather dull pliers. The gold seeds were immediately adopted by many radiotherapists, and are still widely used.

In institutions with relatively small amounts of radium and no radon plant, interstitial needles were employed to a certain extent. However, for reasons which are not clear, most of the needles available in the United States until the last decade were rather strong. Treatments had to be quite short, reactions were often severe, and the techniques did not become popular. In England and France much weaker needles were used, and definite dosage schemes developed, particularly by the Manchester group. In those countries interstitial irradiation was widely used. In America Dr. Charles Martin was the leader in the employment of low intensity needles, and achieved such good reuslts that others followed his lead. With the development of better techniques of implantation and with the simultaneous increase in the number and kind of supportive measures available for the patient undergoing such a drastic treatment, use of radium needles has increased in popularity. In recent years most hospital radon plants have been given up, the radium being put into tubes and low intensity needles, and commercial suppliers relied on for seeds when they are needed. Many radiologists having only strong tubes at their disposal have had the radium transferred to weaker ones.

Gynecological treatements still probably account for the greatest radium use in this country. Several systems of radium distribution have been worked out, here and abroad. The Manchester, Paris, and Stockholm techniques are familiar, and are more or less closely followed in different places. Americans have also developed apparatus and localizing procedures. Dr. Edwin Ernst has been particularly thorough and persistent in efforts to perfect a generally satisfactory applicator. In this field also must be mentioned the work of Pitts and Waterman, and later of Corscaden, in the use of long, low intensity radium needles in parametrial implants.

It was recognized some thirty-five years ago that accurate dosimetry was fundamental to success in any type of radiation treatment. In the case of radium therapy, this had three facets, the accurate measurement of the radium content of the various sources, the determination of the radiation output of each source in terms of an

acceptable dose unit, and a knowledge of the distribution of radiation within the tissues under treatment. The first became the function of the various national laboratories, in this country the National Bureau of Standards. All standards were referred to Madame Curie's original preparations, and it was not difficult to devise suitable procedures for comparing unknowns and standards by ionization measurements.

The determination of dose of radium radiation in terms of roentgens was more difficult. Today everyone is familiar with the statement that a point source of radium, filtered by 0.5 millimeter of platinum, delivers 8.4 roentgens per hour at a distance of one centimeter. The history behind acceptance of this value is long and complicated. Due to the very penetrating nature of the secondary rays from a radium source, the standard ionization chambers which had been developed for 200 kv. roentgen rays were unsuitable. Calibrated thimble chambers gave discordant results. As the difficulties began to be understood, it became evident that the basic measurements ought to be made in very large open spaces. Failla and Marinelli at Memorial Hospital, and Friedrich, at the University of Berlin studied this problem, and Friedrich finally made use of an armory 100×50×22 meters in size to achieve unequivocal results. When the necessary amount of air had been determined, it was evident that the same result should be expected if the air was compressed, so pressure chambers up to 50 atmospheres were tested, with satisfactory results. The final step was to replace air by an "air-equivalent" solid, and use a sufficient thickness of this to make thimble-type chambers.

Once the output of a milligram of radium under specified conditions is known, it is not necessary to calibrate the output of every tube or needle; this can be calculated on a basis of the actual radium content, the geometrical size and shape of the source, and the filtration. Therefore the study of distribution of radiation within the tissues for a particular distribution of sources is much simpler than if large series of measurements had to be made in suitable phantoms with adequate ionization chambers. In fact, the latter would be an almost impossible procedure.

Even before the actual output of a radium source in roentgens had been established, the writer had started a long series of studies on relative amounts of radiation delivered at different points by groups of radium sources. The relative numbers were readily converted to roentgens when a standard value became available. This series of studies has been carried on, with various associates, first at Memorial Hospital, and later at the College of Physicians and Surgeons. In Europe, Paterson and Parker at Manchester developed a system of dosage determination which is at present almost universally used.

No account of the development of radium therapy can be complete without mention of the dangers from handling the material without proper precautions, the early martyrs to the radiations, and the present situation with regard to protection requirements. Soon after the discovery of radium, Becquerel had produced a burn on his skin by carrying a small tube in his pocket. When Burnham went to Vienna to get the 200 mg. mentioned earlier, he carried it in a thin lead wrapping in his overcoat pocket for a few hours. He developed acute nausea within twenty-four hours, and a skin burn which took weeks to heal. By this time, 54 cases of cancer due to roentgen rays had been reported, and it became evident that radium rays were equally dangerous. Dr. Viol, the chief chemist for the Standard Chemical Company as mentioned earlier, died of cancer almost certainly induced by radiation. There have been other cases among medical and technical personnel, and there have been cases of profound and sometimes fatal anemia. There is little doubt that Madame Curie's long illness and death could be attributed largely to the

radium with which she worked so long. Much more common than the fatal cases have been damaged fingers, due often to carelessness or foolhardiness in handling tubes and needles, preparing applicators, and making implantations. It is sometimes said that in these latter procedures overexposure is inevitable, but detailed monitoring of careful operators has shown that this is not the case.

Dr. Failla, at Memorial Hospital, early became concerned with radiation safety, and devoted much time and thought to development of adequate storage safes, shielded handling tools, remote-controlled operations, and general good practice. His devices were widely copied, and in the United States at present most radium preparation rooms are adequately equipped. However no amount of good equipment will compensate for careless procedures, and constant vigilance is necessary as new personnel learn the art and try to develop short cuts.

The International Commission on Radiological Protection has now set up over-all permissible limits for whole body and local exposure, which are not unduly restrictive, and can—and should—be observed by everyone. There is no excuse at the present time for any radiation damage resulting from the clinical use of radioactive materials.

In 1934 artificially produced radioactive substances were discovered, It is now possible to make radioactive forms of every element, and during the past ten years a dozen or so of them have joined the medical armamentarium. Some of them may replace radium in some of its uses, either for economic reasons or because they are actually superior for the particular purpose. Radioactive cobalt and cesium have made possible the development of powerful "teletherapy" units, for the types of treatment aimed at by the early 4–10 gram radium "packs." Radioactive gold grains may substitute for radon seeds, and cobalt seeds and needles may replace or supplement those containing radium. The radium therapist will not suffer from these developments; he will merely extend his horizons.

In 1933 The American Radium Society established the Janeway lecture and medal, in commemoration of Dr. Henry Harrington Janeway, pioneer radium therapist at the Memorial Hospital and an ardent member of the Society during the few years between its founding and his death in 1923. The first Janeway medalist was Dr. James Ewing, who had been responsible for developing the radium supply at Memorial Hospital and for interesting Dr. Janeway in the work. He spoke, in a reminiscent vein, on *Early Experiences in Radiation Therapy*. Subsequent medalists and their subjects have been:

1934—Francis Carter Wood, M.D. *Recent Advances in Experimental Cancer Research*

1935—George E. Pfahler, M.D. *The Protection of the Radiologist*

1936—Curtis F. Burnham, M.D. *Early Experiences with Radium*

1937—Douglas Quick, M.D. *Carcinoma of the Larynx*

1938—Henry Schmitz, M.D. *Historical Retrospect of the Treatment of Carcinoma of the Uterus*

1939—Gioacchino Failla, Sc.D. *Some Aspects of the Biological Action of Ionizing Radiation*

1940—Edith H. Quimby, Sc.D. *The Specification of Dosage in Radium Therapy*

1941—Edward H. Skinner, M.D. *The Philosophy and Economics of Cancer*

1942—William P. Healy, M.D. *The Role of the Gynecologist in the Field of Cancer*

1946—Frederick W. O'Brien, M.D. *Radium Treatment of Cancer of the Cervix, An Historical Review*

1947—Robert S. Stone, M.D. *Neutron Therapy and Specific Ionization*

1948—Sir Stanford Cade. *The Achievement of Radium in the Fight against Cancer*

1949—Charles L. Martin, M.D. *Low Intensity Radium Element Needles*

1950—Otto Glasser, Ph.D. *Evolution of Radiological Physics as Applied to Isotopes*

1951—H. Dabney Kerr, M.D. *Some Thoughts on the Training of a Radiation Therapist.*

1952—A. Purdy Stout, M.D. *Intraepithelial Carcinoma of the Larynx*

1953—Leon O. Jacobson, M.D. *Factors Concerned in Recovery from Radiation Injury*

1954—Lauriston S. Taylor, Ph.D. *Education in Radiation Protection*

1955—Herbert M. Parker, Ph.D. *The Radiological Sciences*

The variety of topics, and the realization that each of them arises from some aspect of the clinical use of radium is indeed illuminating.

The art and science of radium therapy have made tremendous developments in the past fifty years. They are not now static, but are, with the aid of new materials, and methods, about to embark on fresh growth. In such a brief review as this, it is obviously impossible to mention all of the important developments, or to give due credit to all those who have made worthwhile contributions. A complete history would fill a good-sized volume. What has been attempted here is only to furnish a small descriptive background for the story of the progress made during the past half century.

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THE MANAGEMENT OF PATIENTS RECEIVING RADIATION THERAPY*

By LOWELL S. GOIN, M.D.
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"PHYSICIANS," said Lord Francis Bacon, "are some of them so pleasing, and so conformable to the Humour of the Patient, as they press not the true cure of the Disease; and some others are so Regular in proceeding according to Art for the Disease, as they respect not sufficiently the Condition of the Patient." Among the former are those practitioners with the true bedside manner, whilst amongst the latter will be numbered far too many radiation therapists.

Radiation therapy is an art. It is one of the newer arts, founded upon one of the newer branches of science, radiation physics, and the art owes an enormous debt to those men and women upon whose researches has been erected so imposing an edifice. So impressive is the science, so erudite its background, so learned its exposition, that it is little wonder that those who practice the art based upon it are so dazzled by its glory that they fail to perceive some of its clinical applications.

Briefly stated, the thesis of this essay is this: Fascinated and impressed by such purely physical factors as wave length, secondary and scattered radiation, surface doses, tumor doses, exit doses, isodose curves, etc., radiation therapists, absorbed in the fascinating problem of treating a tumor, in the purely physical problem of delivering to a tumor a cancerocidal dose of x roentgens without irreparable damage to the adjacent tissues, not infrequently forget to treat the patient. And yet, it is our purpose, as physicians, to deal with a sentient being filled with fears and doubts, with hope and despair; to treat a sick person, not a disease; to use every means at our command to cure or, at least, to ameliorate disease and to prolong life, or to attempt to render it more bearable.

If we are to pursue the application of this thesis, if we are to recognize the patient as something more than a physical mechanism, then we must attempt to deal with him as a personality requiring not merely repairs but understanding, sympathy, and affection. In short, we must recognize him as a sick human being, not merely as the bearer of an interesting tumor, and must proceed with his treatment on that basis. As a young doctor in country practice I heard frequently a piece of folk-wisdom which remains of continuing value; that if Mrs. Jones would weep bitterly over her dead child she would feel better. This, of course, is a fragment of the process that Freud called "mental catharsis" and is simply a homely way to say that accumulated nervous tensions must be released lest they do grave damage. All of us are busy. We have too many things to do and there are not enough hours in which to do them. Nevertheless, I am persuaded that one of our most important duties is to listen to the patient. The unfortunate people who are undergoing treatment for malignant disease feel a profound compulsion to talk, to talk about their disease, their likelihood of recovery, the fate of a friend who had a like disease, the article just read in a popular magazine. They have problems; they are wrestling with fears; they have just read a popular article about a new miracle drug or atomic medicine. A friend has assured them that the treatment which they are undergoing is not only the wrong treatment but is fraught with danger. "They" used radium on Aunt Hattie, and it just spread the disease. There is no need to

* Presented at the Thirty-sixth Annual Meeting, American Radium Society, Hot Springs, Virginia, March 14–16, 1954.

multiply the examples; all of you know them well. But are you sure that the patient's mind is to be equated with your own logical and well-ordered intellects? Are you sure that these myths, so transparent to you, are as lightly dismissed by the patient? And, if not, what shall you do about them? How shall you reassure the patient and put his or her feet back on solid ground? Well, first of all, you can't possibly do it unless you know what is transpiring in the sick man's mind, and there is only one way to know; talk to him. If he tells you that a friend knows of a patient whose doctor cured him of an identical cancer with two injections, you will not solve a problem by replying correctly—"nonsense." It takes time and mental effort to persuade your patient that there is no secret science; that you and many others know what little there is to be known about the treatment of cancer and that "two injections" are not included in that general body of knowledge and, if you fail to make this point, you may be, unwittingly, a party to an unnecessary death by permitting your patient to drift into the hands of one of the many unscrupulous murderers who have cancer cures. I say, then, listen to your patients. Listen to them patiently and sympathetically, and their gratitude, their affection, and their confidence will be most rewarding.

An ever recurring problem is: What shall we tell a patient who has a malignant tumor? Shall we evade the issue and say that there is a slightly suspicious condition and that a few roentgen-ray treatments are advisable? All too often, this is the verdict that the patient has received. Those who hold with such statements should reflect that there is, in this world, neither happiness nor suffering that ever quite measures up to the anticipation thereof; that nothing in this world is quite as terrible or quite as wonderful as anticipation would have it. There is scarcely a week in which there is not, in some popular magazine, an article about malignant disease. Most of them (all of the honest ones) emphasize the fact that surgery and radiation therapy are our only weapons. Most of them go into some detail about the use of roentgen rays, radium, cobalt, etc., and these articles are widely read. Hence, when a patient is sent for radiation therapy, the patient is well aware that this is a modality commonly employed to treat cancer and begins to wonder whether he or she may have this dread disease. If a patient with a malignant tumor knows the truth, there follows several desirable results: He is saved the sharp cutting pangs of fear that stab those who only wonder if the disease is cancer, and he is encouraged to summon all of his strength and courage to fight for his life, becoming thus much more willing to submit to the arduous and disagreeable days of treatment that lie ahead of him. The fact, known so well to all of you, that radiation therapy is no child's play is not so well known to the patient (and frequently not to the referring physician) and his shock on learning the truth will be materially lessened by the realization that he is fighting for his life.

But, the thoughtful patient may say, can you do nothing to make my ordeal less painful? Can you not lessen the misery that I must endure? Here begins the art of radiation therapy as distinguished from the science; here begins the function of the physician as distinguished from that of the physicist. Time is of the essence, say the lawyers, and we have long been drilled in the thesis that, in the treatment of malignant disease, we have no time to lose. True, we have not, but, if we are to consider the patient, and if we are to evaluate our end results in terms of his survival or at least in terms of his comfort and happiness during his survival, then perhaps it may turn out that a little time spent in preparing the patient for his therapy was not lost and was, in the long run, a distinct gain.

This preparation is both psychologic and physiologic. The psychic state of a good many people who have just learned that they have cancer, or that the cancer previously treated has recurred or has invaded

distant areas, is frequently pretty bad. Most of them are seriously disturbed emotionally; some are in actual depressed states, and some are verging on suicide. An hour spent in calm, sympathetic and rather authoritative discussion with these patients is a very sound investment. I know that you are busy; the point that I am trying to make is that this is an extremely important part of your business. Any of us can, without too much strain, teach a fairly bright resident to calculate tumor doses, but to gain the patient's confidence, respect, and sympathy is an art which is all too rarely cultivated, and which comes only by cultivation.

The purely physiologic aspects of the patient are equally important. Too many patients, presenting themselves for treatment, are in a physical state varying from rather poor to quite cachectic. Their ability to withstand an arduous course of therapy, and to recover not only from the disease but from the treatment is governed to no little degree by their condition when first seen or, rather, when treatment is begun. Many persons with malignant disease are suffering not only from the disease, but from misguided efforts directed toward its cure, as, for example, vegetarian diets, taken under the misapprehension that meat eating has something to do with the existence of cancer; that fruit juices are curative agents, etc. Others, because of physiological disturbances secondary to the diseases are in deficiency states varying from mild to quite severe. These conditions demand attention before the actual therapy is begun if one is to hope for the most beneficial results. Appropriate vitamin therapy, high caloric diets, attention to anemic states, measures designed to improve the appetite and insure adequate sleep are, therefore as important as, or even more important than the prompt beginning of therapy. An example might be the oral hygiene of a patient presenting himself for treatment of a cancer of the floor of the mouth. If he has (as is very likely) numerous carious teeth, some of which are likely to become troublesome in the ensuing year or so, one should delay treatment long enough to have all teeth extracted, beginning the therapy after the gums have healed.

As I have already said, the mental states of these patients are frequently none too good, and one must be psychologist enough to attempt to overcome the profound melancholia and depression so frequently encountered. This is not to be accomplished by a Pollyanna attitude, nor by the Pangloss doctrine that "All is for the best in this best of all possible worlds," but by a calm factual analysis of the situation at hand. A patient with a Stage II cancer of the cervix, for example, should be talked to frankly. No attempt should be made to gloss over the situation, but it should be explained to her that, although the condition is grave, it is not hopeless; that 30 or more out of 100 persons survive and that far from being beaten, she will have, with her hearty co-operation, a fair chance of survival. In general this sort of talk will result in a marked improvement in the patient's mental condition and a determination on her part to win in the ensuing struggle. Also the patient should be told very frankly what lies before her; the long tiresome routine of daily treatment, the discomfort of transvaginal radiation, the disagreeable skin reaction, the diarrhea and urinary frequency, and the hospitalization which will be required if radium is to be employed. With such mental preparation, one encounters no difficulty with the patient whose well meaning friend or relative (and sometimes even the referring physician) tells her that she has been "burned" by roentgen rays, or that she has been made much worse.

During treatment, the patient must be seen very regularly. Questions that have arisen must be answered; misapprehensions must be corrected; encouragement must be given, and the patient must be examined. I was once a witness in a malpractice suit in which "x-ray burns" were alleged. One of the most telling points made by the

plaintiff was that although her skin got redder and redder, and although she complained about it, no one ever looked at it.

I am frequently shocked when, during an interview with a prospective technician, I am informed that she is entirely competent to do roentgen therapy and, in fact, has done all the therapy in a hospital for three years. Roentgen therapy is, in my opinion, a major procedure comparable to surgery. It is something to be undertaken by a physician trained in the art and science, and absolutely not within the province of technicians. I believe very strongly that every patient must be seen every treatment day by a doctor, by a doctor qualified to carry out the treatment and not by a technician who has been given a prescription to fill.

But let us continue with our routine preparation and with the treatment. Having assured ourselves that the patient is in the best possible condition we may commence the active treatment of the disease itself. Almost at once, in many instances, we will find the patient's progress reversed, and our efforts undone by our very efforts. We must, therefore, turn our thoughts to supportive treatment by means of which we may hope to conclude the course of therapy without having inflicted too much injury to the bearer of the disease under treatment. Radiation sickness is a common, distressing, and not infrequently grave complication of treatment, and should be treated by any means which experience has shown to be efficacious. The nausea accompanying radiation sickness naturally limits the caloric intake, and patients lose weight and strength rapidly unless measures are taken to counteract it. With whatever remedial agents employed must be coupled a high caloric diet ample to maintain weight or even to show a gain. Not infrequently the patient is a middle aged woman with a constitutional tendency toward obesity whose vanity impels her to take a limited diet. This tendency must be checked, and in general, these patients should not be permitted to lose weight.

Menopausal symptoms, secondary to pelvic radiation in women are often distressing. They may be controlled without much difficulty by the use of one of the estrogens, but until we know more of the possible hormonal stimulation of cancer, particularly cancer of the breast and of the reproductive organs, their use should be viewed rather dubiously. It is probably better to employ small doses of phenobarbital, e.g., one-half grain two or three times daily, and to avoid the estrogenic substances.

Local manifestations of radiation effect may be most annoying and even quite painful. The dryness of the mouth and the loss of taste sensation so often accompanying mouth and neck radiation may be quite well controlled with fairly large doses of thiamin chloride, 50 mg. or more daily intravenously. Unremitting attention to oral hygiene is essential, and the patient should be instructed to use warm normal salt solution as a mouth wash as frequently as he finds possible. Serious complications such as localized areas of osteomyelitis, may follow dental surgery, often advised by physicians unfamiliar with the effects of radiation of lesions in the oral cavity. Practically speaking, there are no circumstances under which teeth should be extracted within at least one year after radiation therapy of mouth lesions. The patient will do much better to bear his toothache, or his inconvenience in eating, than to subject himself to a possible bone infection. The painful reactions within the mouth are very disagreeable. Nuporal (a trade name for A-buty oxy-cinchoninic acid diethylene diamide hydrochloride) has been very useful in controlling this symptom. It is employed in the form of troches which are allowed to dissolve in the mouth. The drug produces a mild surface anesthesia lasting two or three hours, and has for its only disadvantage the occasional production of nausea.

Among the most constant and most an-

noying of the complications of pelvic irradiation are cystitis, proctitis (with an accompanying diarrhea) and adhesive vaginitis. The prevention of the latter requires the most constant and unremitting care. Regular and systematic dilatation and packing with vaseline gauze are perhaps the best measures once adhesions have formed, but in general they may be prevented by the instillation of cod liver oil in the vagina four or five times weekly. The patient is instructed to procure a soft rubber syringe and to instill two ounces of oil at bedtime and to insert a tampon. A douche may be taken the next morning. The use of stilbesterol in daily doses of 0.1 mg. has been suggested by experimental work, and perhaps deserves trial, but again there is some danger of hormone stimulation to be considered. The ingestion of large amounts of water and citrus fruit juices tend to control the cystitis which, fortunately, is self limited in any case. Small retention enemata of olive oil or of cornstarch are useful in combatting proctitis, while the accompanying diarrhea is best controlled by paregoric and bismuth.

CONCLUSION

1. The therapist must not lose sight of the sick person in his anxiety to treat the disease.

2. The general physical condition of the patient is of the greatest importance, and every effort must be made to improve the general health and to maintain the improvement.

3. The patient's psychic condition must not be neglected.

4. Certain means for combatting common complications of radiation therapy are suggested.

5. The therapist is urged to be as good a clinician as his ability will permit and is assured that his therapeutic results will improve with the increased interest in the sick person committed to his care.

Finally let us not forget the complaint uttered by Plato: "Physicians there be for the soul, and physicians for the body and yet, the two are indivisible."

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DISCUSSION

Dr. H. Dabney Kerr, St. Michaels, Md. It is a pleasure to discuss this paper by Dr. Goin on the management of patients receiving radiation therapy, because it embodies in it almost all of the philosophy which we have been teaching our students and residents for the past twenty to twenty-five years. Dr. Goin's command of the English language and his choice of words have made this paper an exceedingly pleasant one to read. The entire paper is worthy of careful scrutiny and study, but there are a few points in it which I would like to emphasize particularly. The first is that radiation therapy is an art. This, of course, is true not only of radiation therapy, but continues to be true of medicine generally. Unfortunately, the art of medicine is being less and less taught, less and less studied, and consequently patients are more and more treated as cases and less and less as people. In our efforts to apply the latest tables in physics, the latest techniques in high voltage, or supervoltage radiation in order to effect a favorable outcome on the lesion itself, we are prone to forget that these lesions are a part of the patient whom we are treating, and by so doing we may cause irreparable damage or even death of the patient. As Dr. Goin points out, we must remember that we are treating patients and not lesions. His emphasis of the necessity of talking quietly with these patients and preparing them psychologically for what is to happen, is a point well taken. All too many times a patient is told that he has cancer and that operation must be done or that radiation therapy must be given. After such a psychologic blow to the patient is it any wonder that many of us think that these patients can not tolerate the knowledge that they have malignant disease? On the whole, my experience is to the contrary. If one sits down and talks calmly to the patient about his condition, about the probability or even almost certainty that he has cancer, that what we are doing is to attempt to alleviate the condition, that the condition is not hopeless, only in this way will we gain the

confidence of the patient and be able to proceed with the necessary treatment. I am convinced personally that the fear of many physicians to tell patients what they have is not because of the patient's reaction, but because the physician himself does not have the fortitude to sit down and discuss the situation with the patient and the family. This is a difficult but necessary part of the practice of medicine. All of this, as Dr. Goin points out, requires understanding, sympathy and even affection. On the other hand, one must not minimize the seriousness of deep roentgen treatment for malignant disease. The probable and possible reactions should be explained to the patient, because in this way one can build up additional confidence as these reactions appear. In this line also it is important, as pointed out by Dr. Goin, that treatments are given by physicians and not technicians. No treatment should be given without a check made by a physician specializing in radiation therapy.

I am delighted at this timely article by Dr. Goin on a subject which has been very close to my heart for many years, and I am glad that he was the one who chose to write the paper. I commend it to you for reading and re-reading. It should be made an integral part of your practice of radiation therapy, or for that matter, of the practice of medicine, with particular reference to the care of patients with malignant disease.

VOL. 75, NO. 3

APPLICATION OF THE PATERSON-PARKER SYSTEM IN INTERSTITIAL RADIUM THERAPY*

By FERNANDO G. BLOEDORN, M.D.†

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IN the last few years new radiotherapeutic techniques have been developed (supervoltage, rotation, etc.) which represent a positive advance in the treatment of certain cancers. In spite of the evolution of these procedures, there will always be a place for interstitial radium therapy. This method of treatment, when properly applied, offers several advantages not found in beam therapy, even when modern techniques are used.

The radium implantation should be considered as one of the best radiotherapeutic methods of dealing with cancer. Since it is performed under general anesthesia, it is a simple and most accurate procedure for localization of the tumor and its extensions by direct examination. The effective radiation is limited to the tumor bearing tissues only, even when irregularly shaped implants are required. Consequently, higher dosage can be delivered without jeopardizing the tolerance of the tissue, due to the high energy of the radiation and the possibility of better sparing normal tissues.

The supervoltage beam combined with rotation is the radiotherapeutic procedure which gives a distribution of radiation most similar to that of a radium implant. The high dosage is concentrated in the tumor bearing area, but a good portion of the normal tissues are also irradiated to a lower level of dosage. With this procedure the localization of the tumor is not as accurate as in radium implantation, and odd shaped tumors are impossible to handle. When radium implantation is the treatment of choice, better results are obtained than with other methods of controlling the primary tumor. Up to 80 per cent of the cancers of the oral cavity can be controlled locally.

Therefore, it can still safely be stated that *interstitial radium therapy is the treatment of choice for any malignant tumor which requires a rather high dose of radiation, provided the tumor is still localized and can be adequately covered by the implant.* Squamous cell carcinomas of the oral cavity, some skin and lip cancers, and inoperable lymph node metastases are the principal fields of application.

In order to obtain consistent results and to accumulate a fruitful experience, it is indispensable to know the dose delivered. A modern therapist likes to speak in terms of *tumor dosage* when discussing beam therapy. Thus he minimizes empiricism by means of more scientific assessment of his aim. In spite of the limitations and relative inaccuracies of our present procedures, they are the foundations for further development and a means of attaining increased consistency in results. They supply a basic path for the beginner to follow. On the same line of reasoning, it is a useful practice to know the dose delivered by a radium implant. It is known that dosimetry in radium, even in the most ideal cases, will be limited by an error of ±10 per cent. Nevertheless, the knoweldge of the average dosage delivered will save many patients from necrosis or recurrence, particularly in extensive implantation. Experience shows that good results can be achieved without careful dosimetry by spacing the needles 1 cm. apart and using low linear intensity needles. This is true in small implants. As soon as such an empirical procedure is applied to large and complicated implants, the incidence of necrosis is very high.

Since the Paterson-Parker system of radium distribution and calculation of dos-

* Presented at the Thirty-sixth Annual Meeting of the American Radium Society, Hot Springs, Virginia, March 14–16, 1954.
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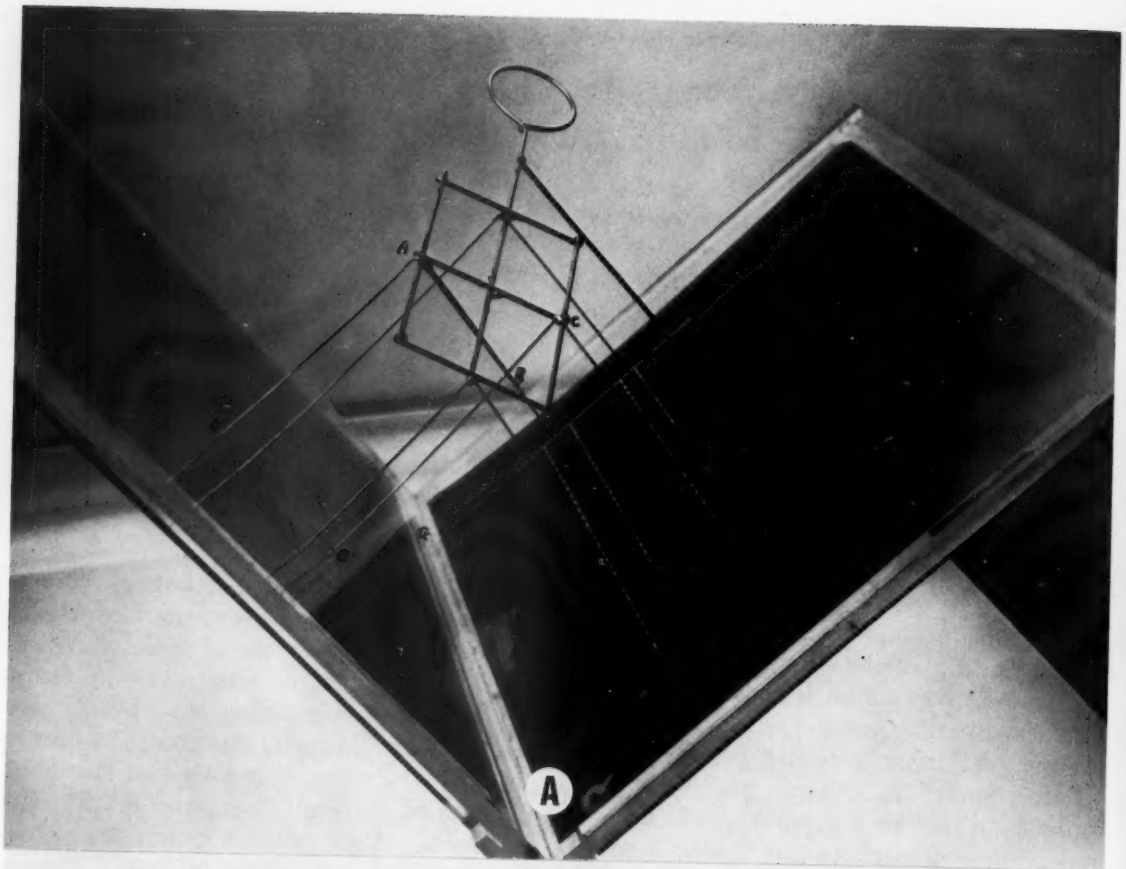
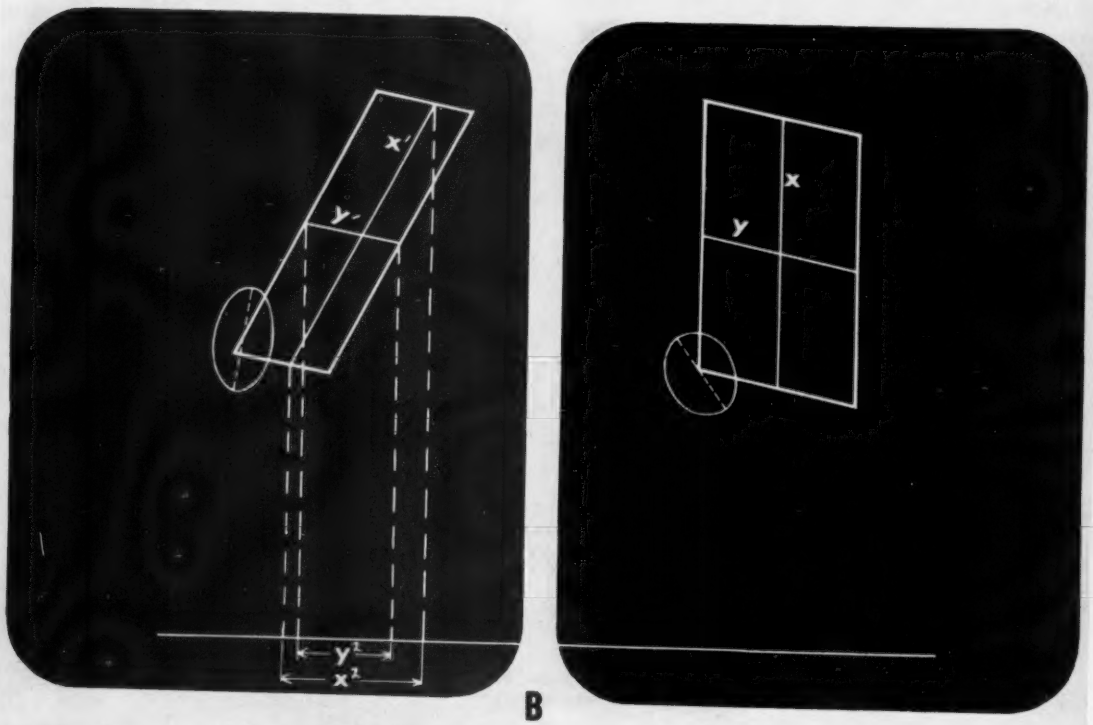


AREA OF SINGLE PLANE IMPLANT



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age is widely known and used in dealing with interstitial radium therapy, its application to clinical problems will be discussed here. It is generally believed that the Paterson-Parker system, although useful for ideal cases, is limited by the use of definite geometric patterns. Nevertheless, unlimited possibilities are practicable if the therapist makes good use of the fundamentals of radium physics and the Paterson-Parker rules for the distribution of the radium load. They give the basis for the knowledge of the shape of the isodose to be obtained in each treatment and the possibilities of adapting the implantation to the need of the individual case.

In our service at the M.D. Anderson Hospital, radium implantation has been the treatment of choice in squamous cell carcinoma of the oral cavity, some advanced cases of skin and lip cancer, and inoperable lymph node metastases, particularly in the neck. In some of these lesions the interstitial radium application was the only form of therapy. In others the implantation was a complement of surgical or roentgen procedures. A high percentage of the lesions were advanced cases.

Interstitial radium therapy in the treatment of cancer is a procedure which very often compares, in aim and results, with very radical surgery. Thus the care in the planning and performance of the implantation should be the same as for a major surgical operation.

The sequence of steps necessary to obtain a satisfactory radium implantation is: (1) establishment of proper indications, (2) careful planning of the arrangement of radium sources, (3) performance of the implantation as planned, and (4) determination of the dose delivered.

(1) *Establishment of proper indications.* Implantation is indicated for the treatment of tumors which are still localized and are of moderate radiosensitivity requiring a high dose of radiation. The region must be surgically accessible and the anatomy should allow a satisfactory coverage of the tumor bearing area by the implantation. The general condition of the patient should be good enough to stand the procedure and a certain level of intelligence is necessary to secure his cooperation.

(2) *Careful planning of the arrangement of radium sources.* Using all possible means of diagnosis, a thorough assessment of the growth and its extensions is made and a

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Fig. 1. Basis of the Parker-Meredith-Stephenson method for dose calculation of implants from roentgenograms. (*A*) Three dimensional reconstruction of an implant from the two perpendicular roentgenograms Suppose we would like to determine from the roentgenograms the dimension *AC*. In the reproduction it can be seen that the direct image on one roentgenogram $A'B'$ is of equal length as the side *AB* on the right triangle *ABC*, after allowance for magnification on the film. The other side of the triangle (*BC*) is equal to the projection of the image of *AC* in the second roentgenogram, upon the "base line" *GF*, after correction for magnification. The "base line" is the line of intersection of the films with a plane perpendicular to both roentgenograms. From the Pythagorean theorem the square root of the sum of the squares of the sides is equal to the length of the hypotenuse *AC*. The other dimensions are obtained in a similar manner and the area of the implant determined. (*B*) Area of single-plane implant, as obtained from the perpendicular roentgenograms. The two axes of the single plane are drawn (height and width). On the image of the ring on each roentgenogram the longest diameter (1*d*) is marked. The magnification factor (*mf*) on each film is equal to the measure of that diameter over the actual diameter (*ad*) of the ring: $1d/ad = mf$.

Height of area is:

$$\sqrt{\left(\frac{x}{mf}\right)^2 + \left(\frac{x'}{mf}\right)^2} = h.$$

Width of area is:

$$\sqrt{\left(\frac{y}{mf}\right)^2 + \left(\frac{y'}{mf}\right)^2} = w.$$

Area $= h \times w$.

From there on the Paterson-Parker tables are used.

complete plan of treatment is outlined. The purpose of planning the treatment so carefully is to determine which arrangement will bring the whole treated volume to the desired dosage level. If possible, a sketch should be drawn including the dimensions, the linear density of loading and the geometric arrangement of the needles to be used.

This plan of treatment will serve a threefold purpose: it will avoid improvisations in the operating room, it will be used as a prescription for the number and kind of needles, and it will facilitate calculation of the dose from the films of the actual implants. When a definite geometric pattern is used, and the rules of distributions of needles are followed, calculation of dosage is always possible.

(3) *Performance of the implantation as planned.* The implantation must always be performed under general anesthesia. It is helpful if the skin or mucosa can be mapped with methylene blue, guided by careful measurements with a ruler. The mapping on the skin will make the time of the actual implantation shorter and will make the technique more accurate.

It should be clearly stated that the efficiency of a treatment must not be sacrificed in order to follow the plan sketched previously. The therapist can vary the plan if necessary during the implantation. The number of cases in which the treatment is altered during the operation will be diminished with thorough examination prior to the implantation, and with increased experience.

(4) *Determination of the dose delivered.* In general, the goal is uniform dosage

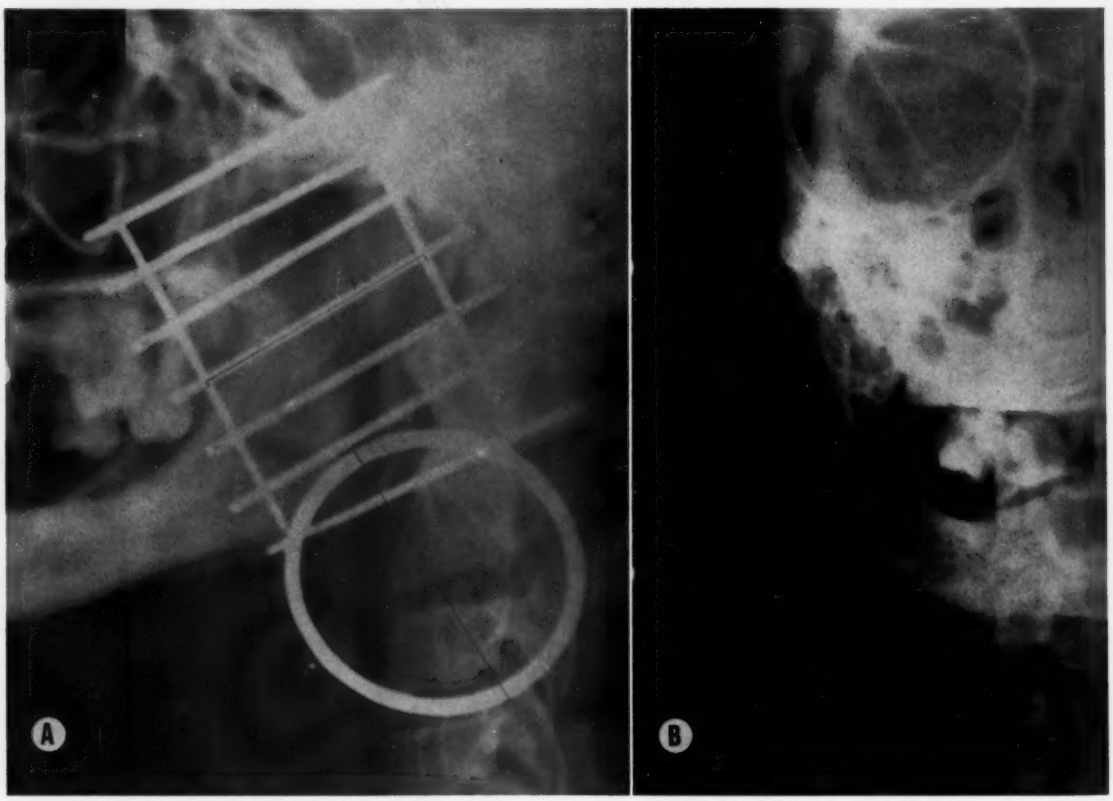


FIG. 2. (*A*, and *B*) Single Plane Implant. Lesion: Large squamous cell carcinoma of the skin of the angle of the jaw. Calculation: As the implant is parallel to one of the films, all the necessary measurements were taken from that film, and allowance made for magnification. The projections on the other films are equal to zero.
Dose: 7,000 r at 0.5 cm. of the plane in seven days.

throughout the irradiated volume. In advanced cases, we try to deliver a higher dose where big masses of tumor are present, and a lesser dose in the surrounding tissues, as in the case of tumor of the parotid, lymph nodes of the neck, etc. Such differences in dosage are of no danger, providing the therapist is aware of them and knows the tolerance of the tissues involved.

THE PATERSON-PARKER SYSTEM: CLINICAL APPLICATION

This system consists of a set of rules for the geometric arrangement and proper distribution of the radium needles in order to attain uniform irradiation. Furthermore, it gives a series of charts to be used in the determination of the dose delivered if the aforementioned rules are followed. The uniformity of dosage achieved has clinical meaning only and is expressed as an average dosage to a given volume of tissue. A recent paper by Dr. Edith Quimby gives a complete analysis of the possibilities for departure from the Paterson-Parker radium distribution using different linear intensities and changes of the peripheral-central ratio.

The Paterson-Parker system would be of little practical value if the different geometric patterns could not be adapted to the varied anatomy of the individual case. It also would be incomplete were it not complemented by a practical method of calculation of the actual dose delivered to the tissues implanted in each case (Fig. 1).

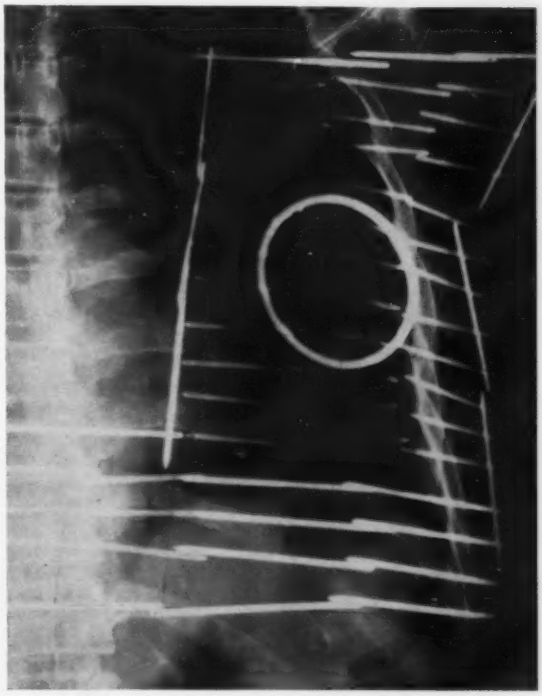
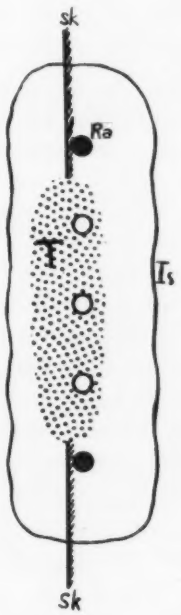


FIG. 3. Large Single Plane Implant. Lesion: Skin recurrences after total mastectomy. Calculation: For the calculation the implant was broken into two partial areas. Applying the Parker-Meredith-Stephenson method the area of each part was determined separately and then added together. The curvature factor was considered. Dose: 5,500 r at 0.5 cm. in six days. This is a good therapeutic procedure when the thickness of the soft tissue covering the ribs is no more than 1.5 cm. It is not advisable in a busy department because of considerable exposure of the operator.



1 SINGLE PLANE

FIG. 2. (*C*) The sketch shows the relationship of the implant with the lesion and the isodose obtained. The solid dot represents full intensity needles; the empty circle represents half intensity needles. Legend for the sketch: Ra = radium, T = tumor, Is = isodose, Sk = skin line.

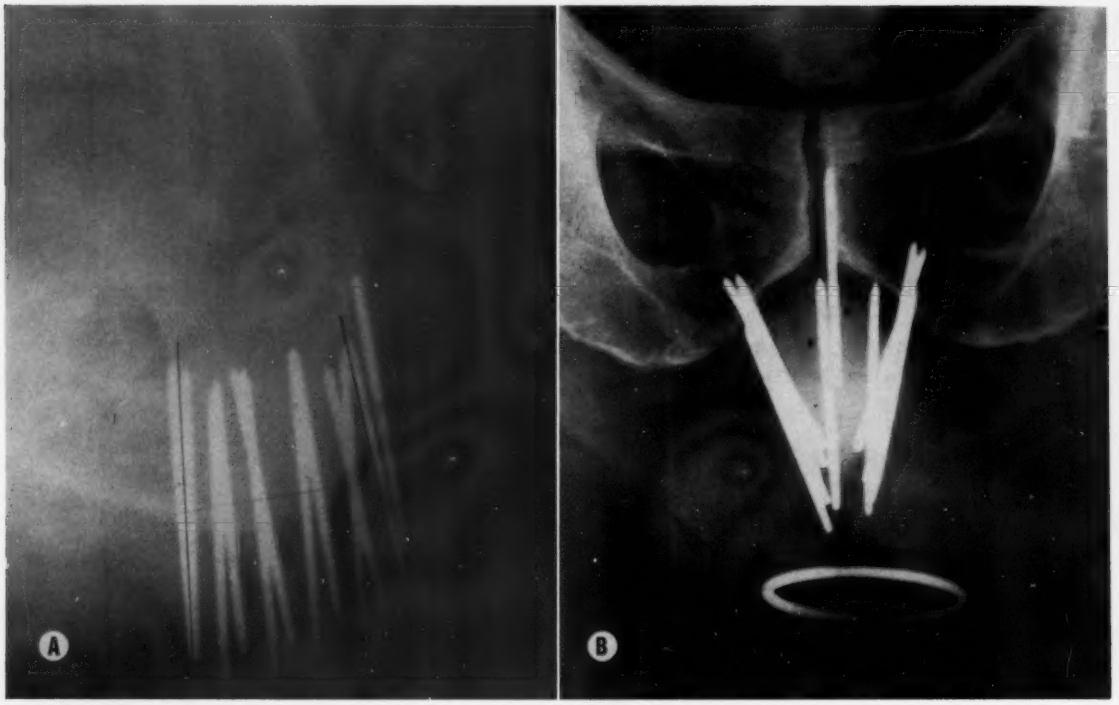


Fig. 4. (*A* and *B*). Double Plane Implant. Lesion: Squamous cell carcinoma of the anal ring. Technique: Implantation in two planes with dumbbell needles (full intensity loading at both end cells, half intensity at the middle cell). To make up for the diminution of the dose between the planes, two full intensity needles were inserted at the top and bottom midway between the planes (*A* and *B*). The divergence of the planes is unavoidable due to the shape of the rectal ampulla. Calculation: The calculation of the dose in the double plane was done following the Paterson-Parker rules. The contributions from the two supplementary needles were calculated from Quimby's tables. Dose: 7,000 r maximum and 5,500 r minimum was delivered in five and one half days.

BASIS FOR THE CHOICE OF THE TYPE OF IMPLANTS

A. SINGLE PATTERNS

1. *Planar or single plane implants.* Single plane implantation, where all the needles are in the same plane, is suited for lesions up to 1 cm. in thickness. Generally the dose is calculated for an area at 0.5 cm. on both sides of the plane of the needles. The method is especially valuable in treatment of squamous cell carcinoma and basal cell carcinoma of the skin, lip, lateral border of tongue, buccal mucosa, and in some cases of carcinoma of the anus, vagina, vulva, bladder, etc. (Fig. 2 and 3).

2. *Double plane implants.* In this type of treatment, the lesion is sandwiched between two planes of needles and the separation between the planes is always more than 1 cm. The procedure is indicated whenever the slab of tissue to be irradiated is thicker than 1 cm. but less than 3 cm. With this method the distribution of the dose is never equal; it is higher close to the planes than it is midway between the two planes, even more so when the separation is greater. Nevertheless, bearing in mind the limitations, double plane implants are very useful in clinical practice in many situations where no other arrangement is possible. The principal indications are: carcinoma of the border and body of tongue, floor of mouth laterally, metastatic lymph nodes of the neck, parotid tumors, carcinoma of the anus, vagina, vulva, skin, etc. The lesions of the lowest portion of the anterior faucial pillar, outermost posterior portion of the border of the tongue, and retromolar trigone are generally well treated with a

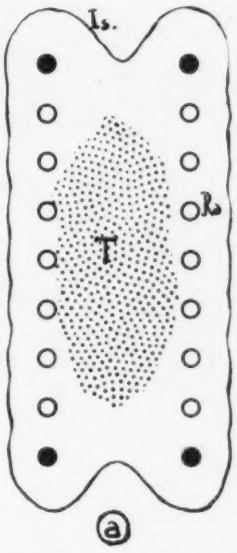


FIG. 4C. *Sketch a*: This shows the relationship between a lesion and an ideal double plane implant. The isodose contour shows the dipping of the dose between planes. Legend: T = tumor, Is = isodose, Ra = radium.

special modality of double plane implantation called the tongue-pterygoid, where one of the planes is implanted through the buccal mucosa and the other in the tongue (Fig. 4 and 5).

3. *Volume implants.* In this procedure, the needles are implanted using either a multiplanar or a cylindrical pattern. A volume implantation is indicated for lesions of more than 3 cm. in thickness. It produces a uniform irradiation throughout the whole area implanted. It is particularly suited for big tumors of the tongue, floor of the mouth, lymph node metastases in neck or axillae, carcinoma of the vulva, especially around the clitoris and urethra, carcinoma of the breast, etc. (Fig. 6).

B. COMBINATION OF PATTERNS

Experience shows that if one uses only simple patterns, the usefulness of the system would be limited to almost ideal early cases. Generally it is the more advanced lesions which derive the greatest relative benefit from interstitial therapy. This is true not only because of the inherent advantages of the radium therapy but because of the disadvantages of roentgen therapy in the treatment of extensive lesions. These include technical difficulties involved in irradiating large areas satisfactorily, particularly in head and neck carcinomas, the limitation of dosage due to the large total volume irradiated and the severity of the reaction produced. Good examples in this respect are the growths of irregular shape and thickness, sometimes with lymph node masses attached or close to the primary lesion, and often with bone involvement.

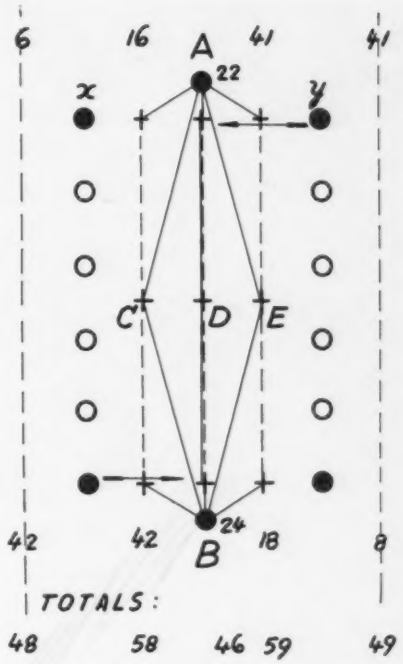


FIG. 4D. *Sketch b*: This represents a sketch of the study of the planes and needle contributions to the irradiated volume (drawn in scale) at the middle of the needles. *x* and *y* are the planes of the implants. *A* and *B* are the full intensity needles in between planes. Contributions from each plane are found at every 5 mm. from Paterson-Parker tables (dotted lines). From Quimby's tables the contribution of the needles is added to points marked with a cross (solid lines). The figures represent the contribution from both planes. Contribution from *A* and *B* needles were not added to avoid confusion by too many figures.

These advanced cases call for a combination of geometric patterns in order to achieve complete coverage of the tumor

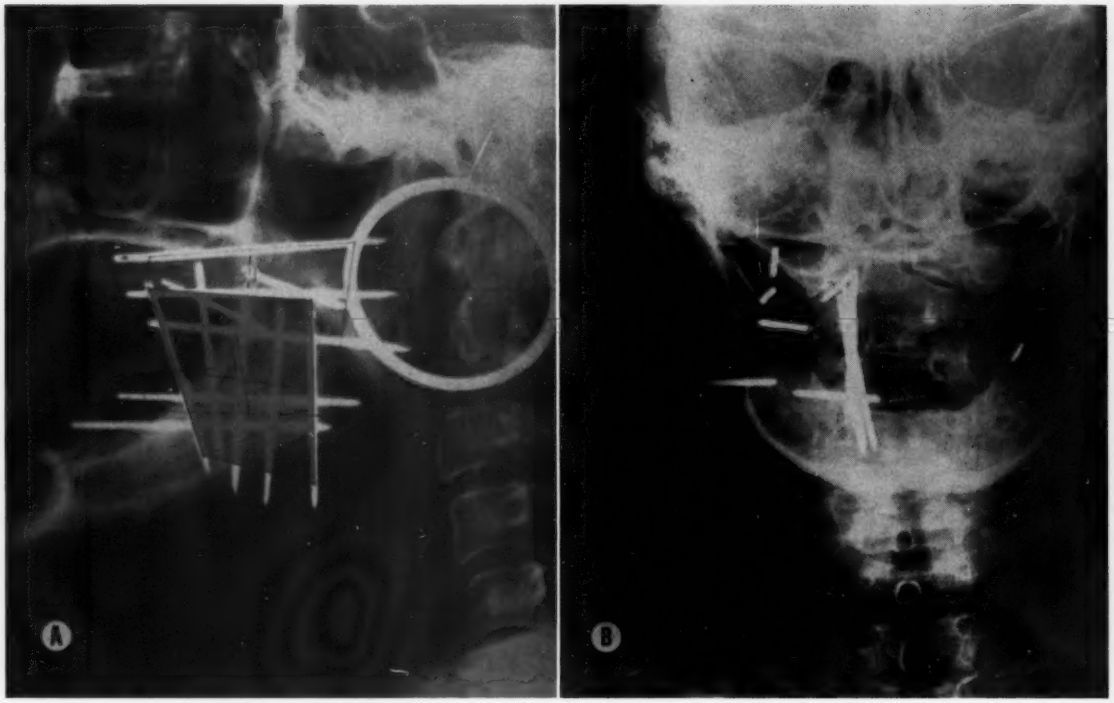


Fig. 5. (*A* and *B*) Tongue-Pterygoid Implant. Lesion: Early squamous cell carcinoma (1 cm. in diameter) on the foot of the anterior faucial pillar. Technique: Double plane implantation. The outer plane (horizontal needles) is implanted from the buccal mucosa, making an effort to bring the middle of the needles close to the lesion. Dumbbell type needles are useful (full intensity loading in both ends, half intensity loading in the middle), instead of half intensity ones. The lingual plane (shaded) has to exceed the lesion both anteriorly and posteriorly. In this case the upper crossing was done partially on the tongue (anterior needle) and partially on the soft palate (posterior needle). Calculation: By following the Parker-Meredith-Stephenson method, the areas and separation were determined. From the Paterson-Parker tables the output per hour at every 0.5 cm. from each plane was found. Dosage: The addition of the outputs gave the dose delivered in six-days as 7,000 r (maximum) and 5,500 r (minimum). Result: Alive and free of disease three years later. Very good function.

bearing area. It is impossible to give rules for the variety of combinations possible, as each case has to be treated as an individual problem. Nevertheless, some possibilities will be enumerated:

1. *A large single plane implant complemented by a smaller double plane implant* used in the neck when a lymph node metastasis of medium size is present (Fig. 7, 8, 9, and 10).

2. *A volume implant combined with a single plane implant* for a tumor of the tongue with invasion of the floor of the mouth and buccal mucosa, or a lymph node metastasis of the submaxillary area (Fig. 11).

3. *A large single plane implant and a volume or multiple plane arrangement* in some cases of carcinoma of the breast.

4. *A two plane implant angulated and overlapping*, in tumors of the parotid area (Fig. 12), and other locations (Fig. 13).

DOSIMETRY

The dosimetry of interstitial radium implantation consists of a preliminary planning which is based on the Paterson-Parker system and of an assessment of the dose delivered by the actual implant in the patient which can be done by several procedures. The most important of these are:

A. *Direct readings.* By means of small chambers and, today, of scintillation meters, placed in proximity to the implants

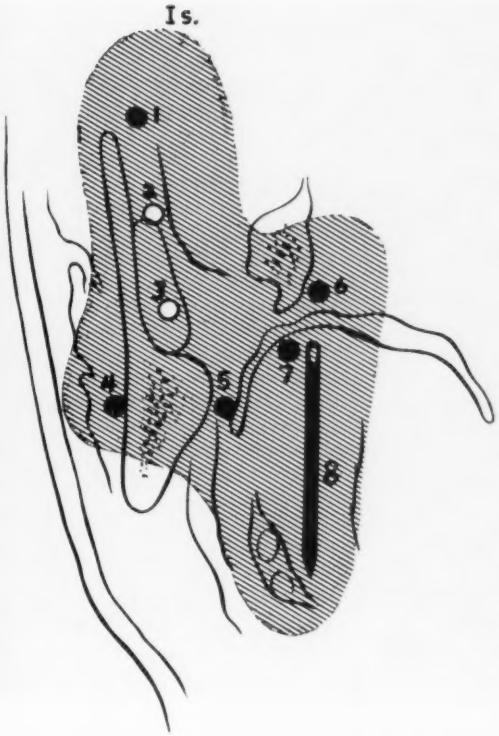


FIG. 5. (*C*) The sketch shows the position of the needles. Needles 1, 2, 3, 4 and 5 make the outer plane, the lower end of which is crossed with two full intensity needles (4 and 5) because the horizontal branch of the mandible does not allow following the plane of the upper needles. Needles 6, 7 and 8 form the plane in the tongue; 6 and 7 are the top crossing needles. *Is* represents the contour of the isodose obtained.

(either inserted in the tissues, or at the surface of the skin and mucosa), the dose is measured at several points. In theory it seems to be the ideal solution, but its use in routine work shows several deficiencies.

1. The chambers or meters have to be very small due to the steep gradient of the dose close to the implant; small chambers are inaccurate in their readings and difficult to manage; and the scintillation meters are new devices, not yet proved in efficiency for this purpose.

2. When the implant is in the depth of the tissues the points where the readings are taken, either on the surface or in the tissues, are difficult to relate to the implant.

B. *Reconstruction of the implant by means of roentgenograms.* Based on roentgenograms (shift-tube or the Spiers' technique) or by means of special devices (Parker and Meredith) the implant is reconstructed outside of the patient. The dose is obtained by:

1. *Direct readings* when the implant is reconstructed with actual radium needles. Small chambers are used for the readings, but the same objections can be made as in the previous procedure.

2. *Theoretical calculations* of area, volume, separation, etc., taken from a reconstruction with dummy needles (Spiers, Parker and Meredith). The Paterson-Parker or Quimby tables are then applied. It can be an accurate procedure, but it is time consuming and probably too elaborate for routine work.

C. *Theoretical or mathematical calculation from roentgenograms taken of the actual implant.* The procedure we have chosen belongs to this group and follows the Parker, Meredith and Stephenson method. It is based on the determination of the area, volume, separation of planes, etc., using roentgenograms of the actual implant. Then the Paterson-Parker tables are applied to find the dose. The principal steps are:

1. *Take roentgenograms* as soon as the implantation is finished and while the patient is still anesthetized. Two roentgenograms are made at right angles to each other, aimed at the center of the implant and at a target-film distance of 36 to 40 inches. *It is better to move the tube without moving the patient.* One of the roentgenograms is taken perpendicular to the largest surface of the implant. In the most convenient incidence, stereoscopic films are also made to complete the determination of the position and distribution of the needles. In some cases, still another roentgenogram is necessary in a proper projection to measure the separation or angulation between the planes.

2. *Carefully study the implant on the films* looking principally for adequate

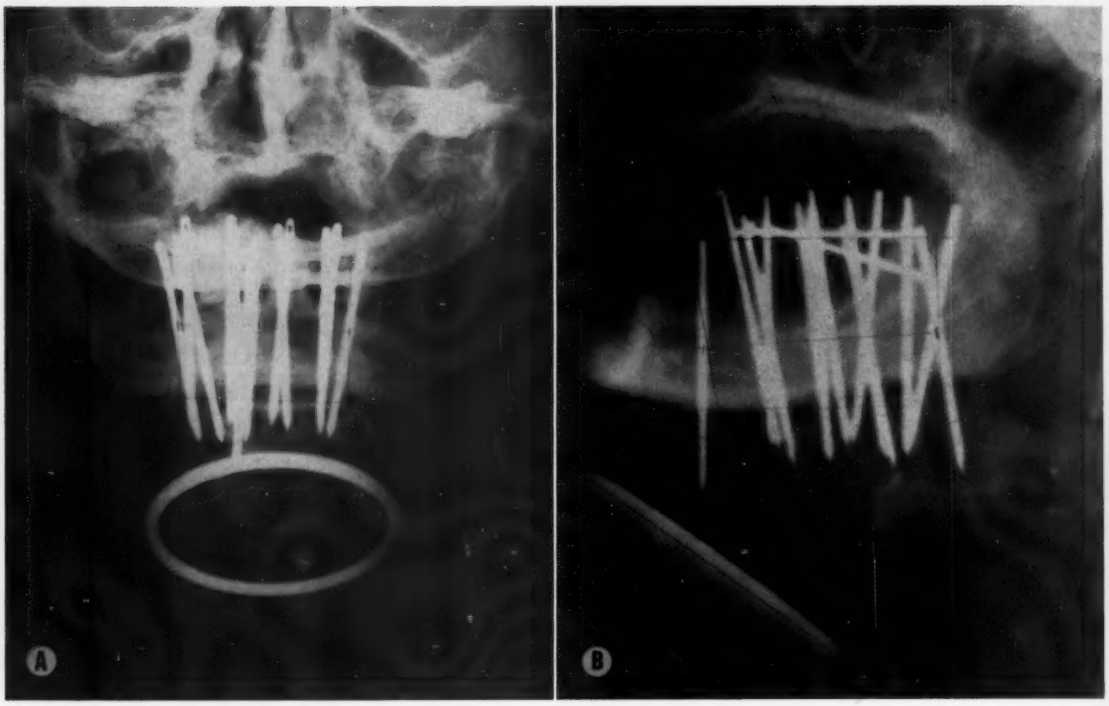
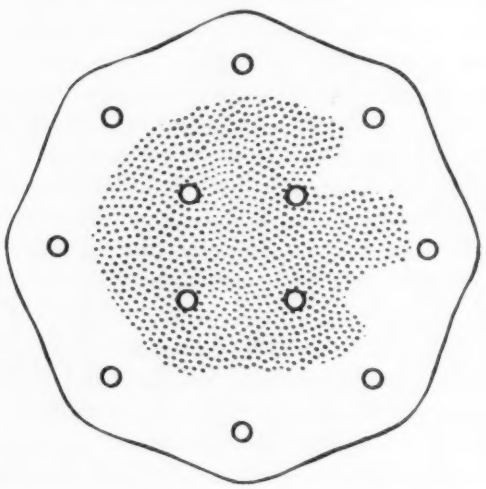


FIG. 6. (*A* and *B*) Volume Implant. Lesion: Squamous cell carcinoma of anterior two thirds of the tongue. Technique: Elliptical cylindrical implant, with crossing of the upper end. Calculation: For the calculation of a volume the diameters are measured directly on each film (allowing for magnification). For the height, the active length of the needles is used if there is no crossing. In this case the height was taken from the upper crossing to the average line joining the lower active end of the needles. Dose: 7,000 r in six days. Result: Alive and free of disease three years later. Mucosa of the tongue smooth and pliable. Very good function.

coverage of the tumor bearing area, geometric patterns, and uniformity (hot or cold spots shown by crowding of needles or big gaps between needles). This is the time to determine if the implant is satisfactory as planned. If modifications are needed, such as addition or subtraction of needles, or removal of the whole implant in half of the time to be complemented with roentgen therapy, they should be decided upon at this time.

3. *Determine the dimensions of the implant* (*area, volume, etc.*) (Fig. 1). This is based on a single geometric problem. If two



3 VOLUME

FIG. 6. (*C*) The sketch shows the relation of the lesion with an ideal volume implant and the isodose so obtained. Notice that only half intensity needles are used and that the needles forming the core of the volume are evenly distributed in the space available. The dose outside of the needles falls off in very steep gradient. This fact is important showing that when a volume implantation is used only the tissues enclosed within the implant are properly irradiated.

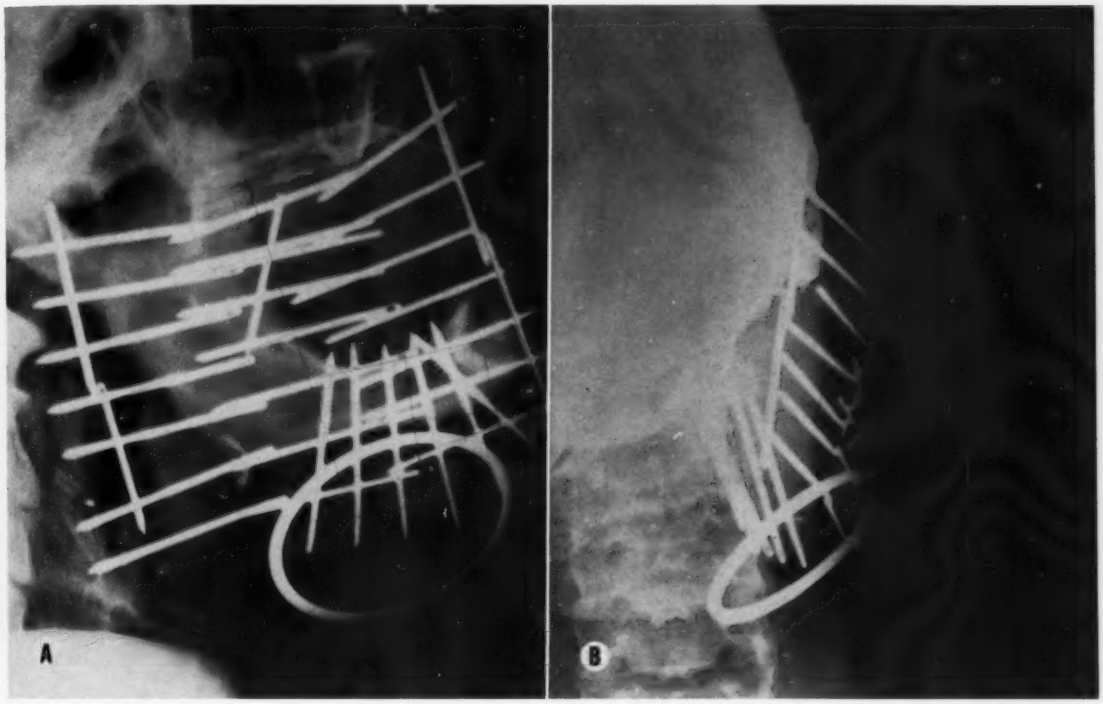


FIG. 7. (*A* and *B*) Implant of Large Superficial Plane with Small Deep Double Plane. Lesion: The patient had postoperative recurrence after partial jaw resection and radical neck dissection for squamous cell carcinoma of the buccal mucosa, gum and floor of the mouth with metastasis to the neck. The recurrence involved the remainder of the floor of the mouth and tissues of the cheek. Technique: A single plane implantation was performed generously covering the disease in the tissue of the cheek. An additional smaller plane was implanted in the floor of the mouth from the submaxillary region. Calculation: The output in each plane at every 0.5 cm. was determined following the Parker-Meredith-Stephenson method and the Paterson-Parker tables. A sketch was drawn in scale with the actual separation between planes. The contribution from both planes was added up in the area where the planes overlapped. Dose: The dose amounted to an average of 7,000 r at 0.5 cm. throughout the whole area, irradiated in six days. The needles in the deep plane were kept in place for a longer time than in the superficial plane in order to obtain a minimum of 6,000 r midway between planes.

roentgenograms of one implant are made at right angles to each other, the dimensions of the area implanted can be found by its projection on both films. Using the projection of the sought dimension on one film, and its horizontal component on the other film, a right triangle can be drawn in which the hypotenuse is the dimension we are seeking. From the Pythagorean theorem, we know:

$$\text{hypotenuse} = \sqrt{(\text{one side})^2 + (\text{other side})^2}.$$

The same procedure is repeated for all necessary dimensions in order to determine the area of the implant. To determine the volume, direct measurements of diameters and height are taken from both films. The *magnification* produced on the films is calculated by placing a metallic ring of known diameter (5 cm. is a convenient size) on the skin of the patient as closely as possible to the implant, and preferably lying in the same plane as the implant in both projections. A ring was chosen because it does not conceal the needles and because there will always be a diameter parallel to any film (the longest diameter shown on the film). By dividing the largest diameter measured on the film by the known diameter of the ring, the magnification factor of that film is found, providing the ring lies close to the implant. If

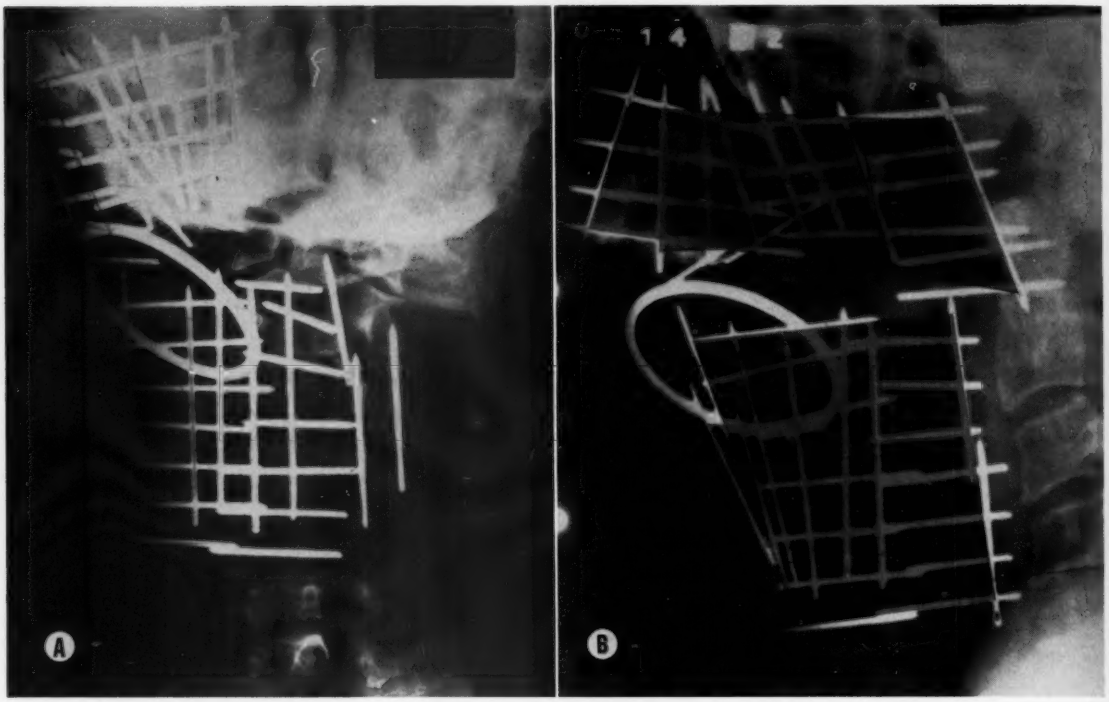


Fig. 8. (*A* and *B*) Complex Pattern of Two Double Plane Implants in an Extensive Postoperative Recurrence. Lesion: The patient had had a jaw resection, radical neck dissection, and wide excision of the cheek. The recurrence infiltrated the whole thickness of the upper flap of the remainder of the cheek, upper lip and upper half of the neck in a shaft-like fashion. Technique: A double plane implantation was used where the tumor was thicker. Calculation: The same procedure was followed as in the previous cases. In the areas of double plane the outputs from both planes were added every 5 mm. Dose: A maximum dose of 8,000 r was given between the planes (shaded), and a minimum dose of 7,000 r at 0.5 cm. from the single planes in seven days. The needles of the superficial planes were removed before the rest of the implant. Result: The patient is alive three years later, free of disease, and with very good cosmetic result.

it does not, a correction formula is applied. (See original papers by Meredith and Stephenson.)

4. *Calculate the dose delivered.* This is done after the actual dimensions of the implant (area, volume, separation of planes, etc.) have been ascertained, by using the Paterson-Parker tables. In the planning and dosage calculation of combined patterns, modifications of the classical radium arrangements are sometimes necessary, taking into consideration the contributions of the planes to each other.

The Parker-Meredith-Stephenson method was chosen for the following reasons:

1. It is applicable to the majority of implants, provided they are planned and executed following definite geometric patterns.

2. It is relatively simple and does not require special mathematical knowledge or specialized equipment. It is a procedure well suited for routine clinical work. A half hour is the average time required for the calculation of one implant.

3. The calculation from roentgenograms leads to a careful study and analysis of the implant. This study allows correction of faulty spots, either by removing or inserting needles. It tends to improve the patterns and uniformity of the implants as demonstrated by the Manchester school.

4. This method makes possible the calculation of the dose at different areas and levels in the majority of complicated patterns, thus diminishing the probability of undesirable effects either from overdosage producing necrosis, or from underdosage

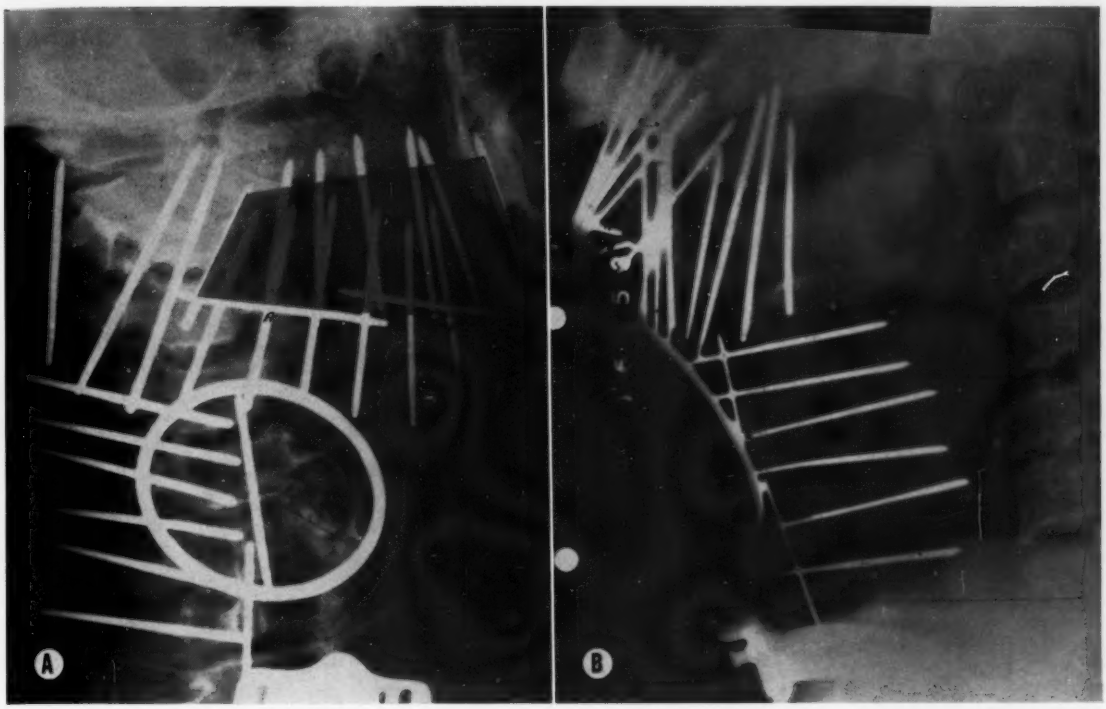


FIG. 9. (*A* and *B*) Large Single Plane and Convergent Double Plane Implants. Lesion: Case of submaxillary mass and shaft-like tumor of the upper half of the neck, recurrent after radical neck dissection. Technique: A large single plane implant covers generously the area of the recurrence. A convergent double plane implant covers the submaxillary mass (shaded). The upper convergence made up for the lack of crossing. The lower crossing was performed midway between the planes (needles A and B). Calculation: The deeper submaxillary plane and the plane of the neck were considered as a single plane. The area was broken into two portions (one for the vertical needles, the other for the horizontal needles); the superficial plane was calculated apart. In the scale sketch with the proper angulation distances between the planes were drawn. The output from each plane every 0.5 cm. was calculated and drawn as a parallel line from each plane. (See Figure 12.) At the points of crossing of these lines the outputs were added. The radium of the crossing needles was shared between both planes. Dose: 7,000 r between planes, 6,500 r at 0.5 cm. off the single plane. The needles in the superficial plane were kept for the time necessary to obtain a dose between the planes of 7,000 r. The needles in the deeper plane remained in place six and one half days.

leading to recurrences.

5. There is close agreement between the dosage calculated, the reaction produced in the tissue irradiated, and the response of the tumor.

6. There has been a satisfactory agreement between the results of this method and the actual measurements taken. We checked the accuracy by making reproductions of actual implants using the shift-tube technique and by taking roentgenograms of dummy implants in different positions and calculating their dimensions by the Parker-Meredith-Stephenson method.

CONCLUSIONS

1. Interstitial radium therapy when properly indicated and performed is a good radiotherapeutic procedure for cancer. The advantages make its displacement by new techniques improbable.

2. If full advantage of the procedure is to be taken, the planning and performance must be as accurate as possible. The steps to be followed have been enumerated.

3. A dosimetric procedure, adaptable to clinical use, will give uniformity in the results, avoiding untoward effects (necrosis or recurrences) in many cases. The clinical experience so acquired will be more fruitful

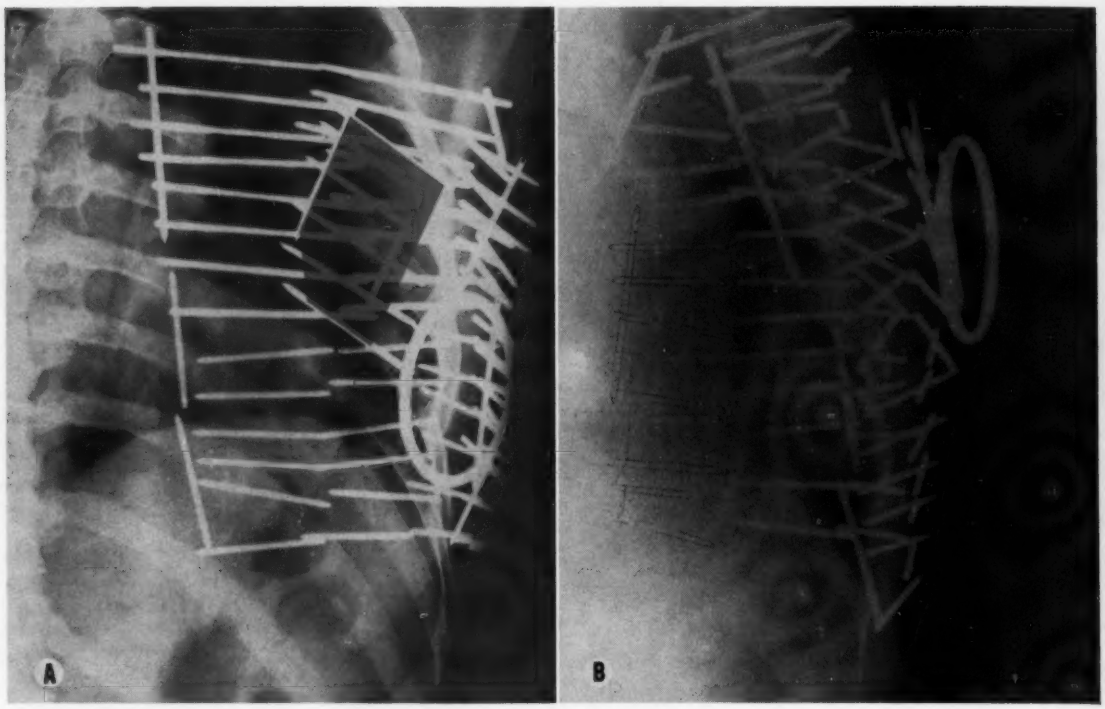
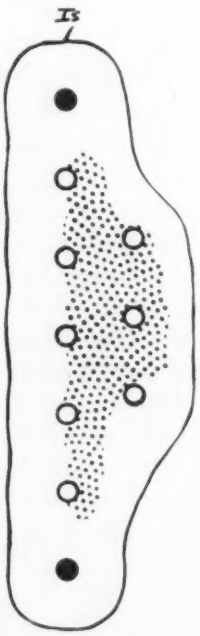


Fig. 10. (*A* and *B*) Single and Partially Double Plane Implants of the Breast and Chest Wall. Lesion: Inoperable adenocarcinoma of the breast with extensive skin involvement. Large single plane implant, overlined in a small area by a double plane implant. Technique: The double plane implant (shaded) is made up of needles of half intensity. If full intensity needles were used for the periphery of the superficial implant, it would yield an unnecessary high dose at this level, when one of the planes is much larger than the other. Calculation: By following the Parker-Meredith-Stephenson method, the areas and separation were determined, and from the Paterson-Parker tables the output per hour was found at every 0.5 cm. The addition of both outputs gives the dose. Dose: A higher dose was delivered between the planes (7,000 r) where the larger mass was present, than at 0.5 cm. from the larger plane (5,500 r), in five days. The needles in the superficial plane were left in place only for the time necessary to make up the difference in dosage. The curvature factor was considered.



and transmissible to others.

4. Uniformity of dosage is not always the aim of a radium implantation. In advanced cases, it is necessary to deliver a higher dose to the bulky components of the tumor.

5. The Parker-Meredith-Stephenson method is a useful and practical one for the dosimetry of radium implants.

SINGLE AND PARTIALLY DOUBLE PLANE

Fig. 10. (*C*) The sketch shows the ideal relation of the planes of needles and the tumor (large single plane with a small superficial plane). In order to obtain the isodose (Is) as required, only half intensity needles should be used in the superficial plane.

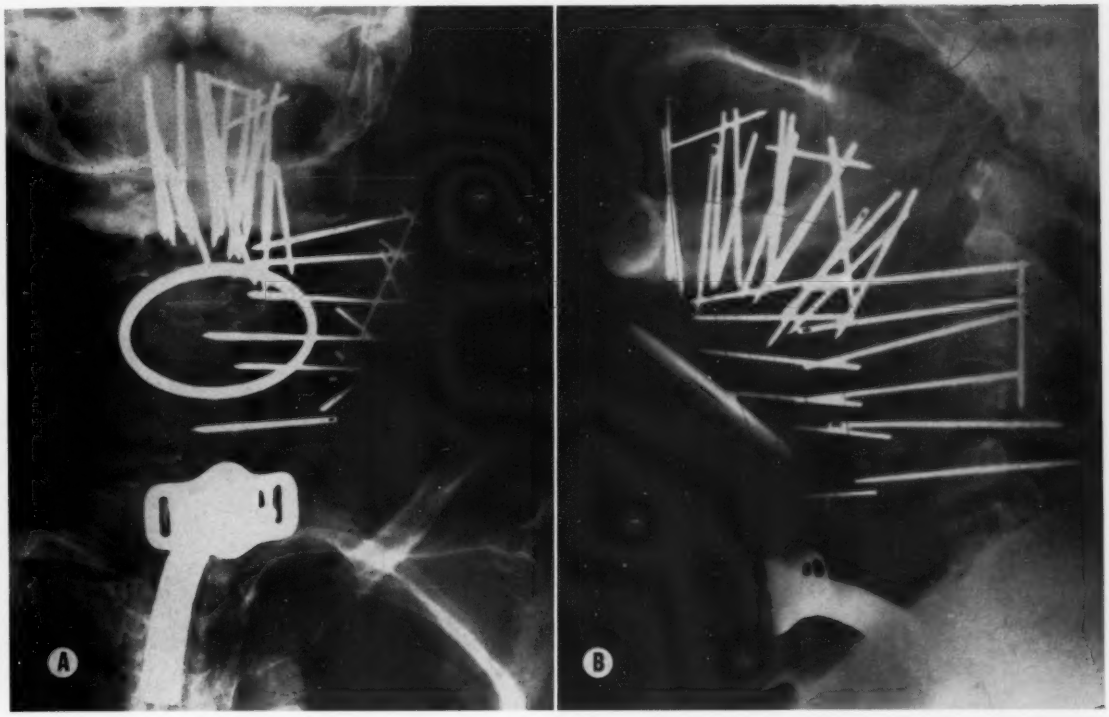


FIG. 11. (*A* and *B*) Combination of Volume and Angulated Single Plane Implants. Lesion: Extensive squamous cell carcinoma involving the whole tongue (anterior two thirds and base), floor of mouth at left, and the lymph nodes in the submaxillary region. Technique: A volume type of implantation was done, including the whole tongue and the left and anterior floor of the mouth. An angulated single plane implant covered the upper neck and submaxillary area. Calculation: The volume was calculated in the usual way. The angulated plane was broken down in two for the calculation of the area. The contribution from the volume to the plane and vice versa was estimated considering the radium of both patterns in its geometric center as point sources (only an approximation). Dose: 7,000 r to the tongue in six days; 9,000 r to the neck at 0.5 cm. off the plane in eight and one half days. Result: Patient is alive three years later, and free of disease with very good functional result.

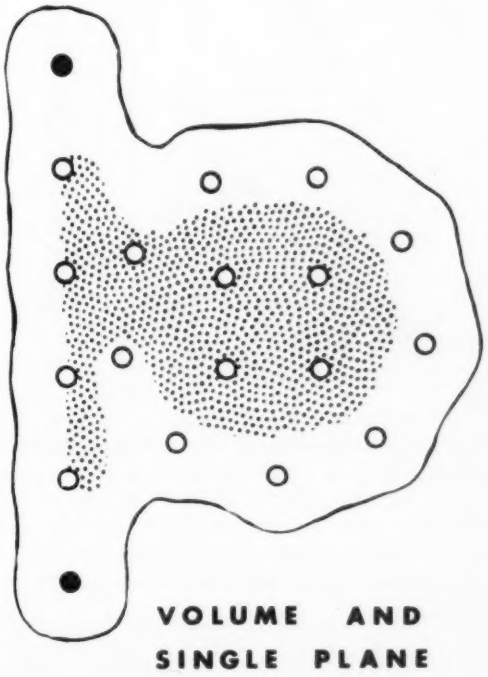


FIG. 11. (*C*) The sketch shows the arrangement of the needles in relation to the tumor.

SUMMARY

The success of interstitial radium therapy of cancer depends upon the following factors: (a) proper indication and careful planning of the implant, (b) delivery of a known average dose of radiation in the tumor bearing tissue, (c) a method of calculation of dose which yields useful clinical data.

The Paterson-Parker system is effective if the above requirements are fulfilled. The system consists of a set of rules and charts which give patterns of geometric arrangements of radium sources, designed to deliver a uniform average dose, with slight fluctuations, throughout the desired volume. The system *per se* would have limited

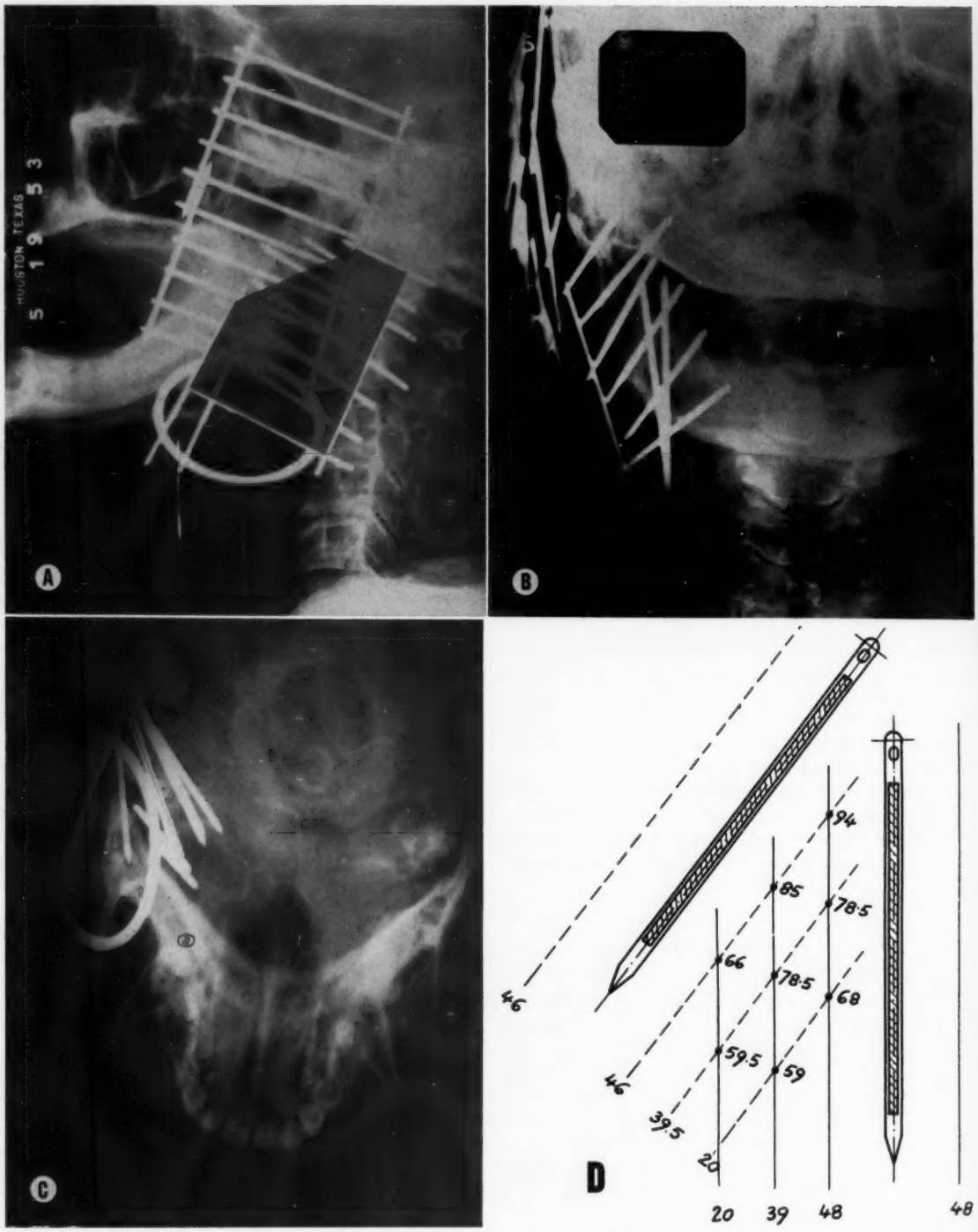


Fig. 12. (*A*, *B* and *C*) Parotid Type of Implant. Technique: Two planes are used, partially overlapping and forming an angle of about 35° between them. The deep plane (shaded) is situated between the spine and the ascending ramus of the jaw, starting as low as necessary. It covers the deep portion of the parotid gland. Two vertical needles (full intensity) inserted from below the angle of the jaw will make for the anterior crossing and increase the dose in the area where the separation between the planes is wider. The superficial plane covers generously the superficial portion of the parotid gland. Its extension will depend on the size of the tumor to be treated. Calculation: For the calculation of the dose, the output of each

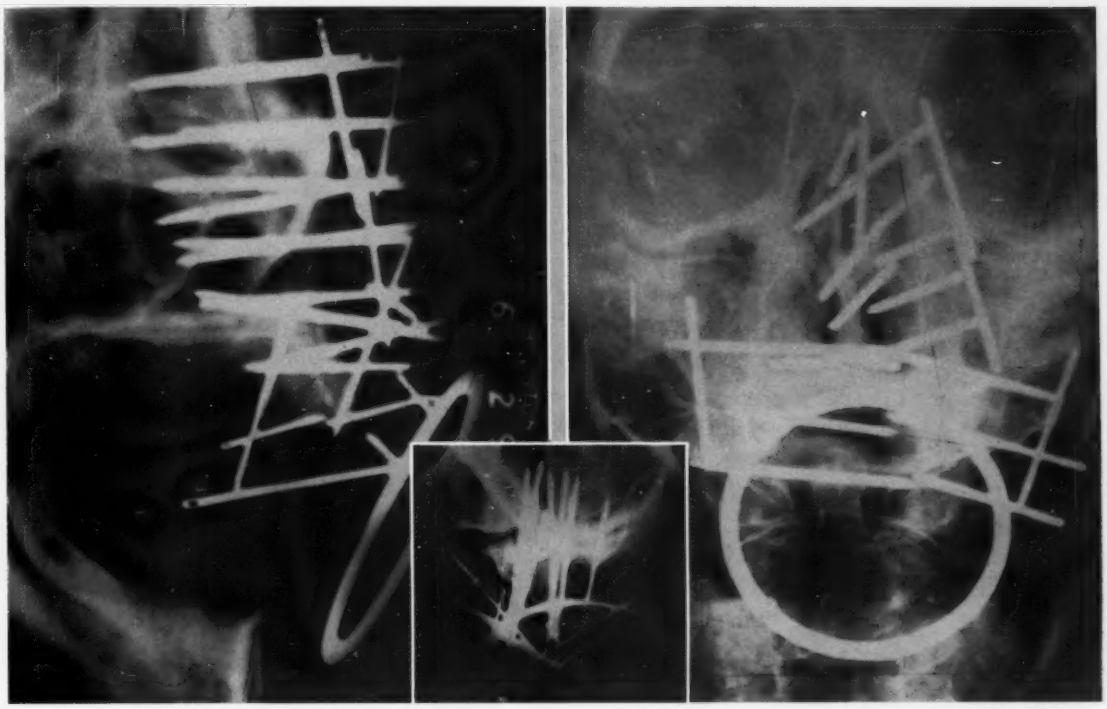


Fig. 13. Complex Pattern Consisting of Two Plane and Angulated Single Plane Implants. Lesion: Basal cell carcinoma of the nose, nasal septum and upper lip. The lesion already destroyed the tip and partially both alae of the nose. Technique: A double plane was implanted through the skin and bones of the nose, sandwiching the septum between the planes. The outer end of each plane was crossed, thus giving a maximum of dose where the disease was more extensive. An angulated single plane covered the lesion of the upper lip. Calculation: The double and angulated planes were calculated separately. The contribution of one implant to the other was estimated considering all the radium concentrated in the geometric center of each implant, as point sources (only an approximation). Dose: 7,000 r (average) in six days. Result: Patient is alive two years later and free of disease with good cosmetic result.

practical value if it could not be adapted to the varying shapes and anatomy of the lesions in individual cases. It must be complemented by a method of calculation of the dose delivered, which is simple to carry out and meaningful in its results.

This study is concerned with:

(1) The clinical application of the Paterson-Parker system and the problems involved in the choice of the type of implant, —i.e., single patterns (whether single or double plane, volume etc.) or a combination of patterns—in order to give adequate coverage of the lesion.

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plane is found in the ordinary way. A film with the technique for the base of the skull (*C*) will be useful for determining the angulation and separation between planes. Dose: A maximum of 10,000 r (portion between planes, where the tumor is generally located) and a minimum of 7,000 r is delivered in seven days at 0.5 cm. from each plane. Indications: This is a useful implant for pre-auricular squamous cell carcinoma of the skin with high carotid chain lymph node metastases; tumors of the parotid, as the only treatment or complementary to surgery; pre-auricular metastases in form of bulky tumor, close to bone invading deeply behind the ascending ramus of the mandible; post-radical neck dissection recurrences, etc. Notice that a "hot spot" is intentionally created where the bulk of the tumor is larger.

Fig. 12. (*D*) The sketch shows the output of each plane at every 0.5 cm. The crossing of the output lines from both planes will give the dose at that point. The addition of dosage is true only for the area of overlapping of the planes.

(2) The discussion of the commonly used method of estimation of the dose delivered. A description of the Parker-Meredith-Stephenson method is given. This was chosen because: (a) it is applicable to the majority of implants, (b) it is simple in routine work and requires no special equipment, (c) there is satisfactory agreement between measurements and calculations, (d) there is good correlation between calculated dose and the reaction observed, (e) it leads to a careful study of the films, which results in improvement of implant techniques and allows the correction of faulty spots either by removing or inserting needles, and (f) it allows the calculation of doses in different areas in complicated patterns.

(3) A series of examples with calculations is given, covering a variety of clinical conditions.

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I would like to express my gratitude to Dr. Gilbert H. Fletcher, Chief of the Department of Radiology of M.D. Anderson Hospital and Tumor Institute, Houston, Texas, who not only made possible this work, but gave me his advice and encouragement and to Mr. G. W. Webb and the staff of the photography department for their efficient collaboration in this work.

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A NOMOGRAPHIC WHEEL FOR THREE DIMENSIONAL LOCALIZATION OF RADIUM SOURCES AND CALCULATION OF DOSE RATE*

By J. GARRETT HOLT, *Physicist*†

IN THE course of interstitial or intracavitary treatment with linear radium sources, it is quite often desirable to know the actual dose rate at a number of selected points within the patient. Anyone who has ever attempted to insert radium sources according to a pre-arranged pattern, will readily attest that in practice the actual distribution of radium sources within the patient often varies considerably from the precalculated geometric arrangement. In order to control the total dose, it is therefore useful to know the actual dose rate at a number of critical points. Unfortunately, these points are usually inaccessible to direct dose rate measuring devices, and one is faced with the problem of calculating the particular dose rates.

The purpose of this paper is to describe a relatively simple, fast and reasonably accurate method of calculation, that is within the scope of the radiologist as well as the physicist.

A wheel nomograph (Fig. 1) has been designed to simplify the problem of calculating the dose rates produced by gamma rays from any number of internal radium sources at a given point. This is particularly useful in the treatment of cancer of the uterine cervix where the dose rate is of interest at points *A*, *B*, *Y*, and rectal and bladder walls.

The wheel consists of two rotating disks of transparent plastic. The top disk has in one quadrant a ruled grid with *X* and *Y* coordinates. The bottom disk contains the reference cross-lines with a protractor and dose rate scale. The latter reads radiation dose rates produced by a linear radium source (active length 1.5 cm.) in r/100 mg.-hr. as a function of the radius of the wheel. The rotating grid, protractor and reference cross-line are used to determine internal distances from bi-planar roentgenograms while the r/100 mg.-hr. scale gives the dose rate for any particular distance.

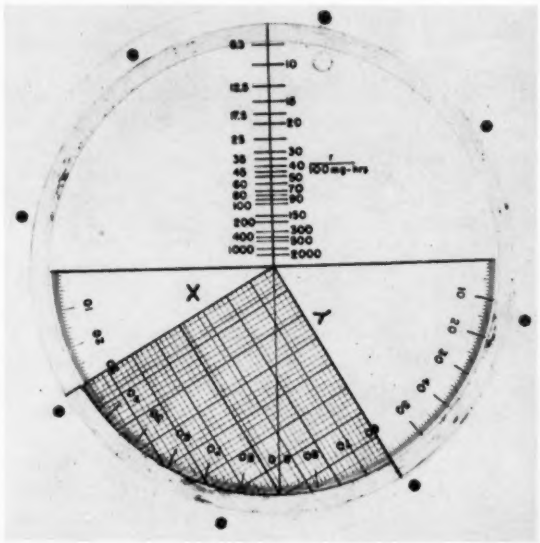

Fig. 1. Nomographic wheel.

DIRECTIONS

Use scribe to mark on the films and pencil to write on the plastic wheel. Pencil may may be readily erased from the lucite surface. If the surface has insufficient bite for easy writing, a pencil eraser may be used to roughen it.

1. Take anteroposterior and lateral roentgenograms of volume of interest by rotating the roentgen tube 90° between exposure (Fig. 2).
2. Determine the magnification (*M*) of

* Presented at the Thirty-sixth Annual Meeting of the American Radium Society, Hot Springs, Virginia, March 14–16, 1954.
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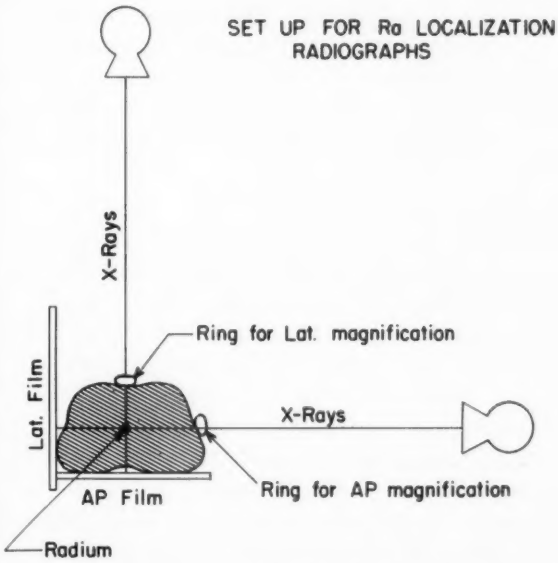

FIG. 2. Set-up for radium localization.

each film and calculate the angles θ_M, where

$$\arccos \frac{I}{M} = \theta_M$$

$$\arcsin \frac{I}{M} = (\pi/2 - \theta_M)$$

3. The control point shall be defined as the point at which the dose rate is to be calculated. If the control point is *not* an anatomic feature, or if it is not determined by markers visible on the film, construct the hypothetic antero-posterior and lateral projections of the control point on both films with consideration of magnification, distortions, etc.
4. Mark the centers of all radium sources

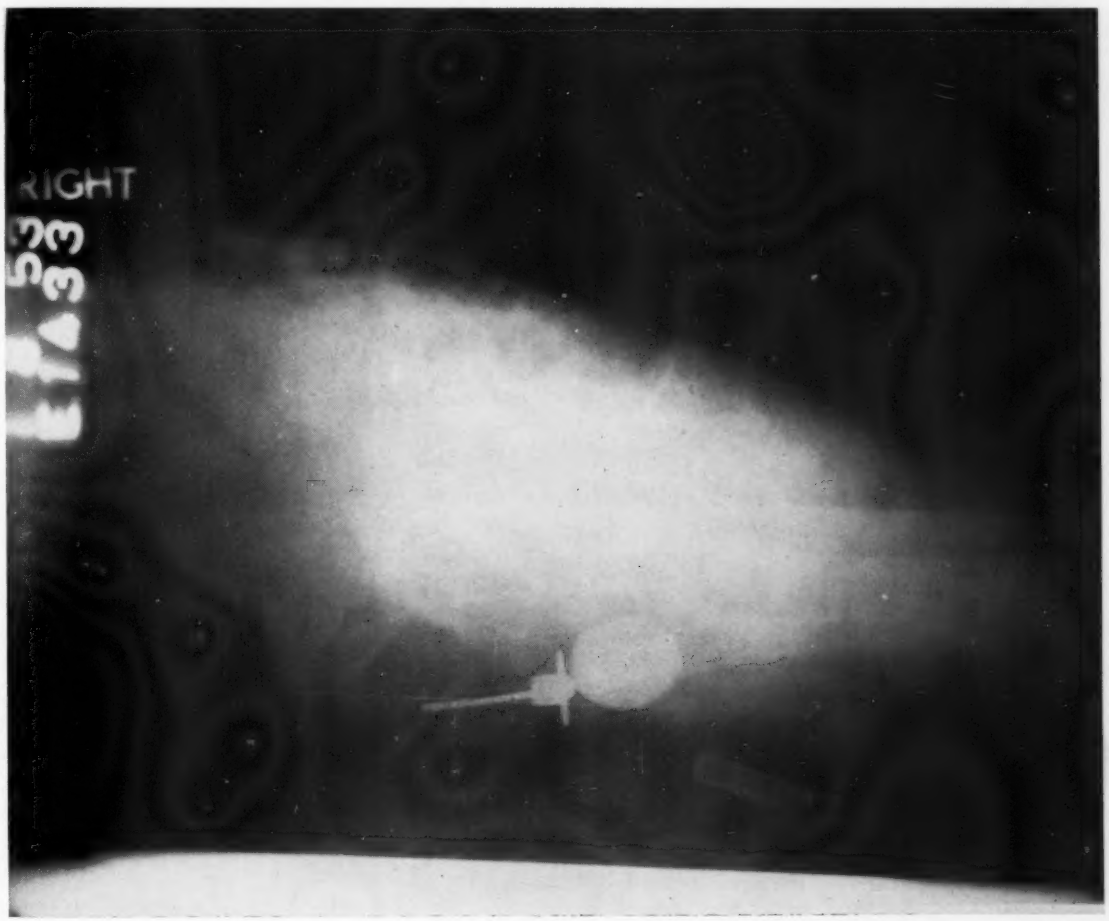

FIG. 3. Lateral view of Manchester ovoids and tandem. Line 1 is constructed through the projection of Point *A*, parallel to bottom of film. *CH* is a small condenser chamber in rectal canal. 1, 2, 3, and 4 are centers of radium sources.

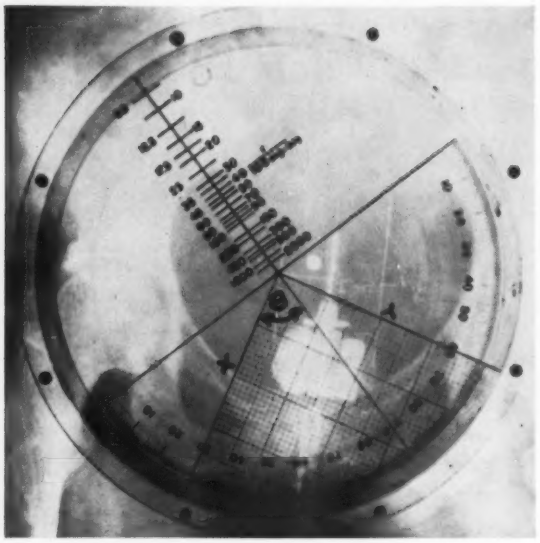

FIG. 4. Wheel in position on anteroposterior film. Note center of wheel is on Point *A;* reference line passes through radium center of left ovoid; θ is set for magnification of 2.0.

on each film and label corresponding points $R_1, 2 \ldots i \ldots$

5. On the lateral film draw a line (l_1) through the projection of the control point and parallel to the plane of the anteroposterior roentgenogram. (This line is usually parallel to the bottom edge of the lateral film.) (Fig. 3).
6. On the grid on the wheel, let the X-axis correspond to the anteroposterior coordinate and the Y-axis correspond to the lateral coordinate.

   The reference line is defined as the line from the center of the wheel (O) to the 90° mark on the protractor. Set the angle θ_X corresponding to the anteroposterior magnification between the reference line and the X-axis in such a way that the reference line falls within the grid. The right side of protractor will read $90° - \theta_X$ on the X-axis, which is the value of θ (Fig. 10) that is derived from the table.

ON ANTEROPOSTERIOR FILM

7. Place the origin of the grid (O) on the control point and tack the wheel in position with a pin through (O) (Fig. 4).
8. Keeping O on control point, rotate the wheel on film until reference line passes through radium center R_i. Mark X coordinate of R_i on X-axis of grid and label X_i. This is k of Figure 7 automatically corrected for magnification.

ON LATERAL FILM

9. Before making measurements on lateral film set the angle θ_Y corresponding to the lateral magnification, between the reference line and the Y-axis. The left side of protractor will read $90° - \theta_Y$ on the Y-axis, which is the value of θ (Fig. 10) derived from the table.
10. Place center of wheel (O) on the line l_1 (see Fig. 3). Shift wheel until reference line is perpendicular to l_1 and passes through radium center R_i. Mark Y coordinate of R_i on Y-axis and label Y_i. This is h of Figure 7 automatically corrected for magnification.

ON WHEEL

11. On grid locate and mark point S_i (X_i, Y_i) that is defined by the inter-

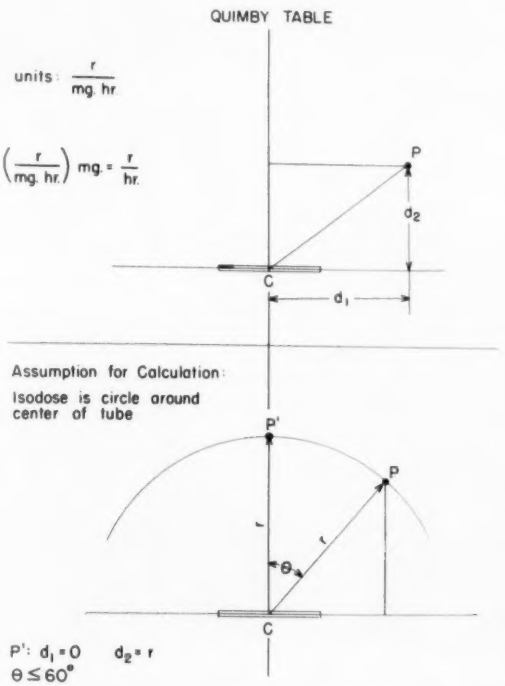

FIG. 5. d_2 and d_1 are needed for entry in Quimby's table of dosage for linear radium sources. Dose rate at P is equal to dose rate at P^1 and d_1 and d_2 may be replaced by r.

section of coordinate X_i and Y_i. Label

$$S_{1,2\ldots i\ldots}$$

Since

$$d=\sqrt{h^2+k^2},$$

distance OS_i is true distance of R_i to control point.

12. Rotate point S_i to scale on wheel and read contribution of radium source R_i to control point in r/100 mg-hr. Multiply by number of milligrams of R_i to read r/hr.
13. Add contribution in r/hr. at control point for all radium sources to find total dose rate.
14. If more than one control point is used, repeat steps 3–13.

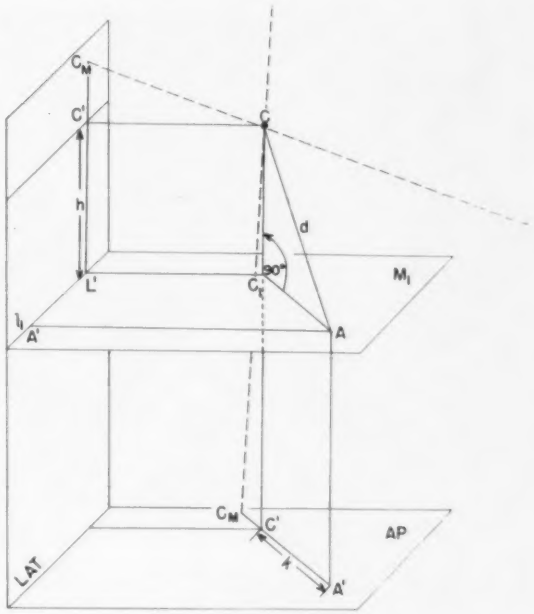

Fig. 7. Construction for mathematical arguments for localization.

THEORY

ASSUMPTIONS, SIMPLIFICATIONS AND PRINCIPLES

1. With certain restrictions, isodoses form spheres around the centers of linear radium sources, which project into circles in any one plane (Fig. 5).
2. A diagnostic roentgen tube renders a perspective projection of an object on film. This appears magnified on the film (Fig. 6).
3. It is possible to convert a metric measurement made in the plane of a perspective projection into a length that would have been the result of a parallel projection (orthographic projection), e.g., measurement on a film divided by the magnification factor results in the true length.
4. It is possible to utilize the principles of three dimensional localization by means of bi-planar parallel projection, provided that the proper corrections are made.

Given. Points A and C which may represent the center of the radium source and the point at which the dose is to be calculated (Fig. 7).

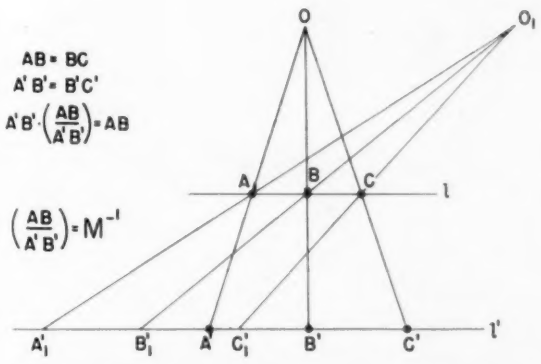

Fig. 6. Perspective projections. O and O_1 may be replaced by focal spots of diagnostic rubes.

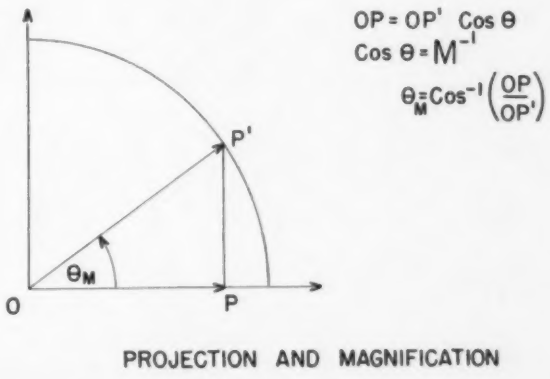

Fig. 8. OP', the magnified distance, may be projected into OP, the true distance.

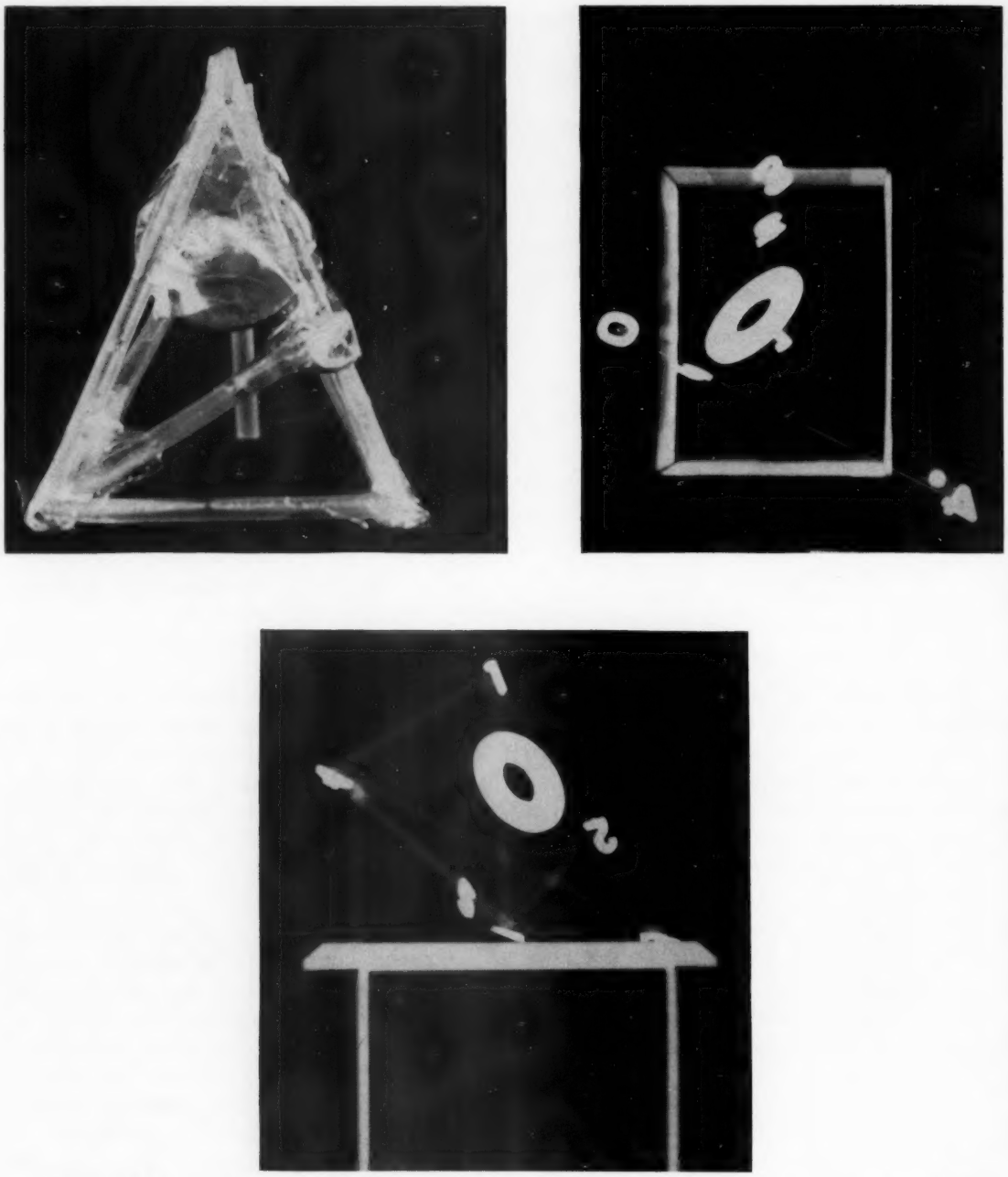

FIG. 9. Photograph and anteroposterior and lateral roentgenograms of three dimensional model that was used to test the accuracy of the wheel.

Wanted. Distance $CA = d$

A. By parallel projection on the lateral plane project C and A into C' and A' respectively; on the anteroposterior plane project C and A into C' and A' respectively.

B. Construct plane M_1 through point A and parallel to anteroposterior plane.

C. Plane M_1 cuts lateral plane in line l_1.

D. Let line CC' cut plane M_1 at C_1; C_1 projects into L^1 on line l_1.

E. Distance $(CA)^2 = (C_1A)^2 + (C_1C)^2$ but,

$$C_1C = L'C' = h$$
$$C_1A = C'A' = k$$

therefore,

$$d = \sqrt{h^2 + k^2}$$

F. By perspective projection C' will be at C_M but since we are interested only in metric length and not in orientation.

$$C_MA'/M = k$$
$$C_ML'/M = h$$

where M is the magnification.

$$\frac{1}{M} \leqq 1$$

In words, we can shrink each dimension to its true size by dividing by its magnification.

5. Since $1/M \leqq 1$ it can be set equal to a sine or cosine value.

$$1/M = \text{Cos}\,\theta_M \qquad \frac{1}{M} = \text{Sin}\,(\pi/2 - \theta_M)$$

$$\frac{1}{M} \leqq 1$$

For the magnified distance OP' (Fig. 8) there exists an angle θ_M which will project OP' into OP, the true distance, where

$$\theta_M = \text{arc cos}\,\frac{1}{M}$$

$$(\pi/2 - \theta_M) = \text{arc sin}\,\frac{1}{M}$$

6. The r/mg.-hr. scale was constructed from Quimby's tables[1] for an active length of 1.5 centimeters and 0.5 mm. Pt filter.

To locate the internal sources, anteroposterior and lateral roentgenograms are taken by rotating the roentgen tube 90° between exposures, the patient remaining stationary. The average magnification for the anteroposterior and lateral roentgenograms is determined by conventional methods.

DISCUSSION

The validity of the wheel centers around the assumption that the isodoses around a

SET COORDINATE AXIS ON θ ON PROTRACTOR

M	θ	M	θ	M	θ	M	θ
1.01	82.0	1.26	52.5	1.51	41.4	1.76	34.7
1.02	78.6	1.27	52.0	1.52	41.2	1.77	34.4
1.03	76.4	1.28	51.4	1.53	40.8	1.78	34.2
1.04	74.2	1.29	50.8	1.54	40.5	1.79	34.0
1.05	72.3	1.30	50.3	1.55	40.2	1.80	33.8
1.06	70.6	1.31	49.8	1.56	39.8	1.81	33.6
1.07	69.2	1.32	49.2	1.57	39.6	1.82	33.3
1.08	67.8	1.33	48.8	1.58	39.4	1.83	33.1
1.09	66.5	1.34	48.3	1.59	39.0	1.84	32.9
1.10	65.5	1.35	47.8	1.60	38.7	1.85	32.7
1.11	64.3	1.36	47.3	1.61	38.4	1.86	32.5
1.12	63.2	1.37	46.9	1.62	38.1	1.87	32.3
1.13	62.2	1.38	46.4	1.63	37.9	1.88	32.2
1.14	61.3	1.39	46.0	1.64	37.6	1.89	32.0
1.15	60.4	1.40	45.6	1.65	37.3	1.90	31.8
1.16	59.6	1.41	45.2	1.66	37.1	1.91	31.6
1.17	58.7	1.42	44.8	1.67	36.8	1.92	31.4
1.18	58.0	1.43	44.3	1.68	36.5	1.93	31.2
1.19	57.2	1.44	44.0	1.69	36.3	1.94	31.0
1.20	56.4	1.45	43.6	1.70	36.1	1.95	30.8
1.21	55.7	1.46	43.2	1.71	35.8	1.96	30.7
1.22	55.0	1.47	42.8	1.72	35.6	1.97	30.5
1.23	54.4	1.48	42.5	1.73	35.3	1.98	30.3
1.24	53.8	1.49	42.2	1.74	35.1	1.99	30.2
1.25	53.2	1.50	41.8	1.75	34.9	2.0	30.0

FIG. 10. Conversion table, to find the angle θ that corresponds to a given magnification.

linear radium source are spheres in space, or circles in a plane (Fig. 5). This is more or less true provided that the distance from the point of interest to the center of the radium source is at least one-half the active length, and one excludes the small regions near the ends of the radium needle that are bounded by two solid angles of 60° ($\pi/3$) the apices of which meet at the center of the needle. The excluded regions are symmetrical around the long axis of the needle and do not extend beyond a few centimeters along the axis. There is reasonable agreement with measurements taken with a scintillation crystal isodosimeter. The isodose surfaces curve in somewhat towards the end of the radium needle. This effect depends on self-absorption and naturally varies among different radium sources. The assumption of a spherical isodose surface would lead to a somewhat higher dose rate near the end of the needle than the true dose rate and would, at least, be on the safe side.

The r/mg.-hr. scale on the wheel becomes somewhat difficult to read when the distance from the center is less than 2 cm. However, in most cases, the distances measured will exceed 2 cm. In any case, the accuracy of determining dose rates cannot be guaranteed at very close distances by theoretical methods due to individual differences in self-absorption of radium sources.

The r/mg.-hr. scale of the wheel is calculated for an active source length of 1.5 cm. However, as one can readily verify from the Quimby tables, the scale can be used between active lengths of 1.0 cm. to about 3 cm. without introducing a significant error, provided the shortest distance is not less than one-half the active length of the source.

There arises the question, "How accurate is the bi-planar method of localization?" A three dimensional model was placed on a box for elevation and anteroposterior and lateral roentgenograms were taken (Fig. 9). Distances within the model were calculated by means of the wheel and then compared with the actual measurements taken from the model. In no case did the maximum error of the calculated distances exceed the inherent error of the measurements on the model, which was about ±1 mm.

An average planar magnification was used for the spatial arrangement of points within the model. This did not seem to introduce significant errors in measurements.

A theoretical consideration shows the following inherent error of measurements made by assuming an average magnification.

If the target film distance is H cm. and the plane for which the magnification is chosen lies h cm. above the film and parallel to the film, then the magnification will be:

$$M=\frac{H}{H-h}$$

assuming a target film distance of 100 cm. (H = 100) and h = 10 cm., then

$$M=\frac{100}{90}=1.11$$

If we suppose an average spread of 5.0 cm. that is ±2.5 cm. above and below our average plane:

$$M=\frac{100}{87.5}=1.14\ h=12.5\text{ cm.}$$

$$M=\frac{100}{92.5}=1.08\ h=7.5\text{ cm.}$$

This means an inherent error in the anteroposterior and lateral measurement of ±3 per cent or an error of ±4 per cent in the measurement of the true distance in three dimensions.

A ±4 per cent error in distance at 1.0 cm. from the radium source will result in the following error in dose rate. (The values are taken from Quimby's table.[1])

1.0 cm. = 670 r/100 mg.-hr. 100%

1.04 cm. = 640 r/100 mg.-hr. 95.5%

0.94 cm. = 700 r/100 mg.-hr. 107%

At a distance of 5.0 cm. from the radium source:

5.0 cm. = 33.0 r/100 mg.-hr. 100%

5.2 cm. = 30.1 r/100 mg.-hr. 91.2%

4.8 cm. = 35.5 r/100 mg.-hr. 107%

Therefore, an error of ±4 per cent in the distance measurement yields an error of dose rate that is less than 10 per cent.

Since the points are generally evenly distributed above and below the average plane, the error tends to decrease in practice.

Calculations in patients were checked whenever possible by intracavitary Farmer-Baldwin chambers and a scintillation probe, and were found to be within reasonable agreement.

All things considered, the accuracy of the wheel in dose rate calculations is believed to be better than 10 per cent, provided one stays within the limitations imposed by the assumptions. This accuracy seems to be within the limits of clinical application.

SUMMARY

A wheel nomograph has been designed to simplify the problem of calculating gamma ray dose rates from any number of internal radium sources to a given point. The wheel can be readily adapted for use with other isotopes by making the appropriate corrections on the r/mg.-hr. scale. The nomographic wheel was designed to be used by the radiologist and to provide him with a simple tool for dose rate calculation. It is hoped that this method will encourage people to check radium dosage by actually calculating dose rates to a number of selected points. In the case of intracavitary use of radium in the vagina or uterine canal, the maximum dose to the nearest rectal wall and the bladder may be readily estimated by outlining the rectal canal and the bladder, and later calculating the respective dose rates. In practice, the wheel has been a great time-saver. It has reduced a chore of four to six hours to about twenty minutes work, and it has easily lent itself to many applications.

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Department of Radiology
Duarte, California

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1. Quimby, E. H. Dosage table for linear radium sources. *Radiology*, 1944, *43*, 572–577.

A GRAPHICAL METHOD FOR THE LOCALIZATION OF RADIUM SOURCES FOR DOSAGE CALCULATION*

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THE calculation of radium dosage requires accurate localization of the radioactive sources in the tissues, unless their position closely follows a prearranged plan such as the Paterson-Parker system. Too often a satisfactory pattern is not accomplished, making it necessary to calculate the dosage rate at several points in the tumor and surrounding tissue. These may be points in the center of the tumor, on the margin of the tumor, or at sites suspected of receiving an exceptionally high or low dosage rate. All such points are designated as critical points.

The principal difficulty in localization develops because the images of the sources on the roentgenogram are magnified and their relative positions distorted. This is a characteristic of roentgenographic projection due to the divergence of the projecting roentgen rays from the nearby focal spot, which is practically a point. For the purposes of localization a more desirable projection of the implant would be obtained by rays parallel to each other and perpendicular to the plane of the film. This is orthographic projection, which is free of both magnification and distortion. From a pair of orthographic projections of an implant taken at right angles to one another, the determination of true distances is possible. The purpose of this paper is to describe a graphical method by which a roentgenogram made with the usual divergent roentgen ray beam can be corrected to the orthographic view.

A clinically acceptable localization method should be simple, accurate and fast. It should avoid mathematics and require relatively little in costly apparatus or special training of the technician. Finally, it should be versatile, in that it can be applied to sources both near and far from the critical point.

The use of graphics appears to meet the requirements of radium localization. The theoretical analysis is described in Part I. A description of the necessary apparatus and a detailed step by step working outline of the practical method is set forth in Part II.

PART I. THEORETICAL ASPECTS OF THE PROBLEM AND ITS GRAPHICAL SOLUTION

Howard W. Vreeland, M.S.

For the purpose of discussion consider a hypothetical implant of four needles. Figure 1 illustrates how the point source roent-

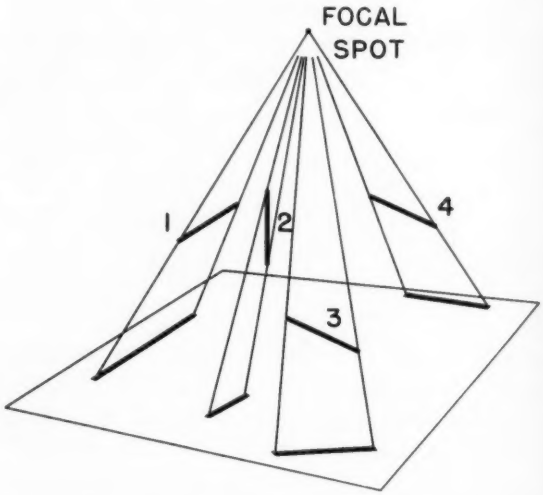

FIG. 1. Roentgen-ray projection of an implant demonstrating the effects of the divergent beam: needle no. 1, parallel to the film, is elongated; needle no. 2, perpendicular to the film, projects as a line; parallel needles no. 3 and no. 4 appear non-parallel.

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genographic image of the implant would be cast on a film. Note the following characteristics of the image: (a) needle no. 1, which is parallel to the film, appears as a line which is longer than the true length of the needle; (b) needle no. 2, which is perpendicular to the film, projects as a line; (c) needles no. 3 and no. 4, which are of equal length and parallel to each other, are seen as non-parallel lines of different lengths.

The dotted lines in Figure 2 are an orthographic projection of the same implant. The projecting rays are all perpendicular to the plane of the film.

It is apparent that spatial relationships are more clearly illustrated, for now: (a) needle no. 1, which is parallel to the film, appears in its true length; (b) needle no. 2, which is perpendicular to the film, projects as a point; (c) needles no. 3 and no. 4, which are of equal length and parallel to each other, are seen as parallel lines of the same length.

More important, however, is the true representation of the space dimensions of the implant. An orthographic projection on one plane will show two of the three space dimensions of the implant. A second orthographic projection on a plane perpendicular to the first will show the third dimension. Thus two orthographic projections of an implant made on planes 90 degrees apart completely define the implant

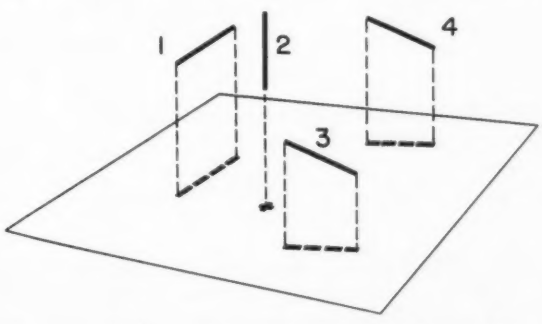

FIG. 2. Orthographic projection of the implant shown in Figure 1, in which the projecting rays are all perpendicular to the film: needle no. 1, parallel to the film, appears in true length; needle no. 2, perpendicular to the film, projects as a point; parallel needles no. 3 and no. 4 appear parallel.

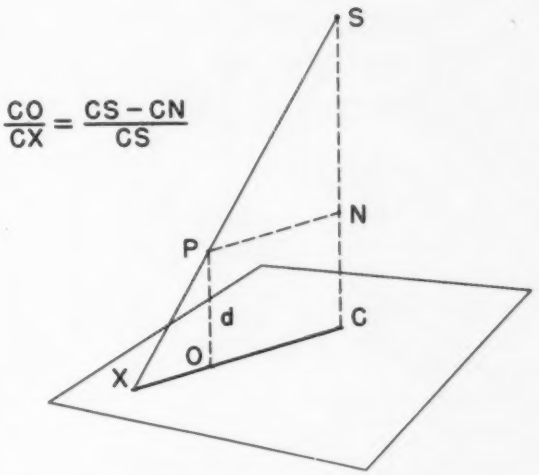

FIG. 3. Relationship between orthographic and roentgen-ray projection. In this diagrammatic representation, the roentgen-ray image of a point P is X, whereas its orthographic projection would be O. Point O is on the line between X and C, the latter being the place on the film where the central ray of the beam falls. The position of O along this line is given by the proportion shown in the figure. In practice, $CS = 100$ cm., and $CS - CN = d$, which is the height of point P above the film.

and provide sufficient information to localize the sources accurately.

The principle by which the routine roentgenogram can be corrected to its orthographic equivalent is evident from an analysis of Figure 3, in which

- S is the focal spot of the roentgen-ray tube.
- P is one of the end points of an implanted needle located a distance d above the film.
- X is the roentgen-ray projection of P.
- O is the required orthographic projection of P.
- C is the projection of the central ray, *the one roentgen ray which falls perpendicular to the plane of the film.*

All of these projecting rays lie in a plane and point O is on the line joining points C and X. If NP is parallel to CX, the following relationship holds:

$$(1) \qquad \frac{NP}{CX} = \frac{NS}{CS}$$

But $NP = CO$, and $NS = CS - CN$, there-

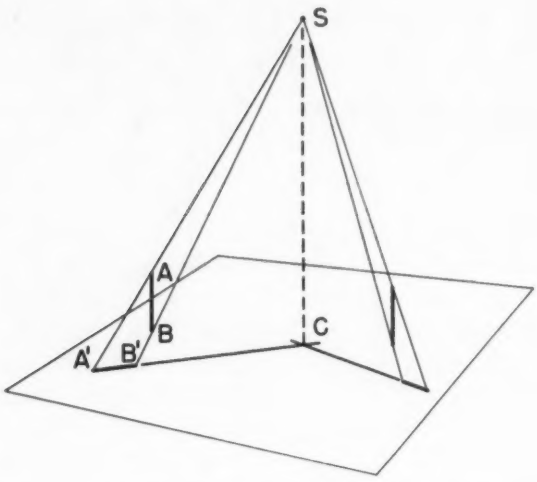

FIG. 4. Method of locating point *C*. The roentgen-ray image of line *AB*, perpendicular to the film, is a line (*A'B'*) which, if extended, passes through point *C*. The images of two such lines can be extended to locate point *C*.

fore:

$$\frac{CO}{CX}=\frac{CS-CN}{CS} \tag{2}$$

Since $CN=OP=d$, the true distance of the point from the film, and $CS=100$ cm. in practice,

$$\frac{CO}{CX}=\frac{100-d}{100} \tag{3}$$

This means that if the roentgenographic image of a point is connected to point *C* by a line drawn on the film, the orthographic projection of the point can be located along the line by the proportion (3) stated above. By this method, the end points of the sources in an implant can be established in orthographic projection.

In practice, for the correction of a given point to its orthographic equivalent, a knowledge of the following is required:

(a) The focal spot to film distance. This is predetermined or measurable in every instance.

(b) The distance of the point from the film. This is accurately determined in the practical procedure presented in Part II of this discussion.

(c) The location of point *C*. This can be achieved by means of a principle illustrated in Figure 4.

In Figure 4, *AB* is a radiopaque line perpendicular to the plane of the film, or parallel to the central ray, *SC*. The roentgen rays through points *A* and *B* strike the film at points *A'* and *B'* respectively. A line through *A'B'* is the intersection between triangle *SA'B'* and the plane of the film. Because the central ray *SC* is parallel to line *AB*, *SC* is also in the plane of the triangle *SA'B'*. *SC*, therefore, must strike the film at some point along the intersection line through *A'B'*. If a second line similar to *AB* is projected on the film, its extended projection will cross the line through *A'B'* and locate point *C*.

PART II. PRACTICAL APPLICATION

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EQUIPMENT

The following is a description of equip-

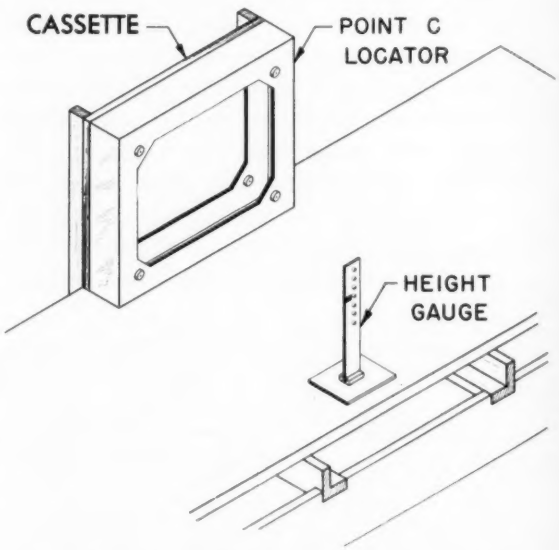

FIG. 5. Modification of hospital stretcher for taking special roentgenograms. The film cassette, point *C* locator and height gauge are shown in position for the lateral view. The height gauge is placed twice as far from the film as the estimated position of the implant. In making the anteroposterior roentgenogram, the height gauge is removed and the cassette and locator inserted along the tracks under the table. See Figure 6.

ment similar to that used by the authors in some 40 cases with satisfactory results. An allowance of $200.00 is suggested for materials and labor. Specifications of this equipment lack details which a competent machinist will be able to fill in provided the function of each component is made clear to him.

A general view of the apparatus is shown in Figure 5. An ordinary radio-transparent hospital stretcher is fitted with a wooden framework. This accommodates a standard 14 by 17 grid-front cassette in either a horizontal or vertical position about midway between the ends of the stretcher. A plastic box, called a point *C* locator, is held in close contact with the film cassette in both positions. Figure 6 is an end view of the assembly in section showing the relative locations of the two positions of the film cassette and point *C* locator. The angle between these should be $90° \pm 1/2°$ and the dimensions should be held to $\pm 1/16''$. In addition, Figure 5 shows a plastic scale, called a height gauge, which stands upright on the stretcher top. The seven divisions on this scale are marked with BB shot imbedded 2 cm. apart, with the middle shot located exactly 32 cm. above the plane of the horizontal film. This particular division is identified with a lead marker.

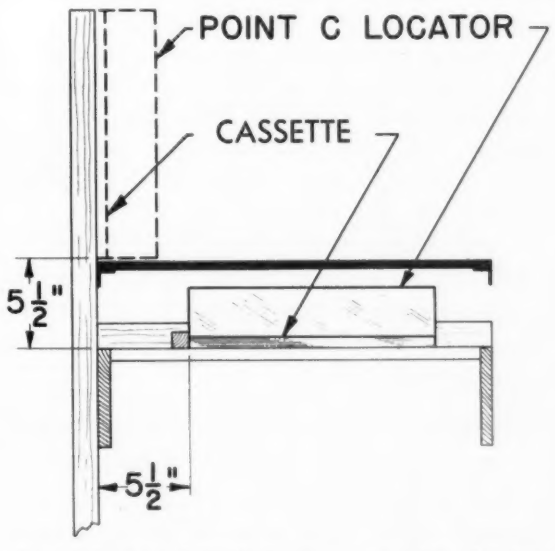

FIG. 6. Section through roentgen-ray table, showing the relative locations of the two positions on the film cassette and point *C* locator.

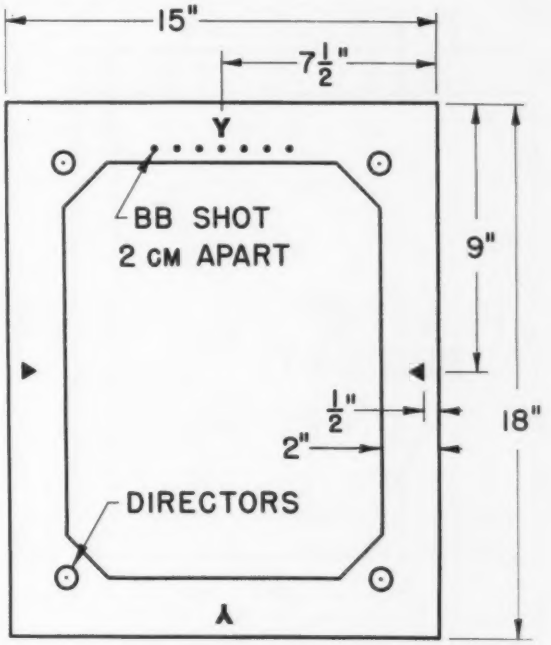

FIG. 7. View of the point *C* locator showing the location of the *V-V* and *Y-Y* lead reference markers and BB shot imbedded in the bottom surface.

Figure 7 shows the pattern of lead markers which are imbedded in the bottom of the point *C* locator. The *V-V* and *Y-Y* markers define lines respectively perpendicular and parallel to the long dimension of the stretcher. The seven BB shot, spaced 2 cm. apart, comprise what is called the true scale. The middle shot is on the *Y-Y* reference line and is therefore 32 cm. from the plane of the opposite film in either position of the point *C* locator. These markers should be imbedded deeply enough into the bottom surface of the point *C* locator so that there is uniform, close contact between the locator and the face of the cassette.

Figure 8 is a section through a corner of the point *C* locator showing the details of director pins. A pair of these is located in each of the four corners. These short steel pins within plastic bushings define the end points of a line perpendicular to the bottom surface of the locator. It is of the utmost importance that each pair of director pins be aligned as nearly perpendicular

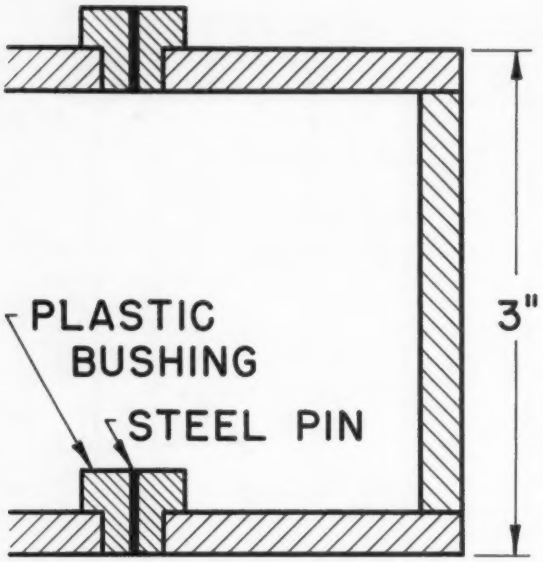

FIG. 8. Section through a corner of the point *C* locator showing details of director pins. Each pair of director pins defines the end points of a line perpendicular to the bottom surface of the locator.

to the bottom plane of the point *C* locator as the machinist can make them.

ROENTGENOGRAPHY

An anteroposterior and right lateral roentgen study is made as follows:

1. Determine the general location of the implant within the patient.
2. Place the patient on the stretcher in the supine position.
3. Insert the grid-front cassette in the horizontal position with the point *C* locator resting squarely on top of it, and with the true scale (BB shot) toward the head of the patient.
4. Make the anteroposterior exposure with a focal spot to film distance of 100 cm.
5. Without moving the patient or stretcher, set the cassette in the vertical position with the point *C* locator in front of it and with the true scale again toward the head of the patient.
6. Measure the approximate distance of the center of the implant from the plane of the vertical film. Position the height gauge on the stretcher top so that it is *twice* as far from the vertical film as is the center of the implant. It is desirable that the image of the height gauge falls along the side of the film which is toward the foot of the patient.
7. Make the right lateral exposure with a focal spot to film distance of 100 cm. It is not particularly important that the 90° shift of the roentgen-ray tube be exact.

SELECTION OF CRITICAL POINTS

As soon as the roentgenograms of the implantation are available, a conference should be held by the radiotherapist, the physicist and any other clinician who might aid in the selection of critical points, such as the gynecologist in a case of pelvic cancer. The purpose of this conference is to define the limits of the tumor bearing volume on the films, identify the needles and visualize the pattern of the implant. On the basis of this, points can be selected within the tumor or in the normal structures adjacent to the tumor where a knowledge of dosage is desirable. These can be marked on the film and are the critical points. In addition, certain points can be chosen at the time of radium application and made visible on the roentgenograms by the insertion of dead radon seeds.

In areas where such aids are not feasible, opaque catheters, bony landmarks or the sources of radium themselves can be used to designate critical points. In the graphical method, it is very simple to project into space from a visible reference point and establish a critical point at the desired distance and direction.

Once the critical points, three or four in the average case, are selected one is ready to proceed with the constructions for localization of the individual sources to each critical point.

GRAPHICAL CORRECTION AND LOCALIZATION

The graphical solution following the selection of critical points is a routine procedure. The actual steps in this operation are given in complete detail below in a manner which makes it unnecessary to understand the theory. All of the work is

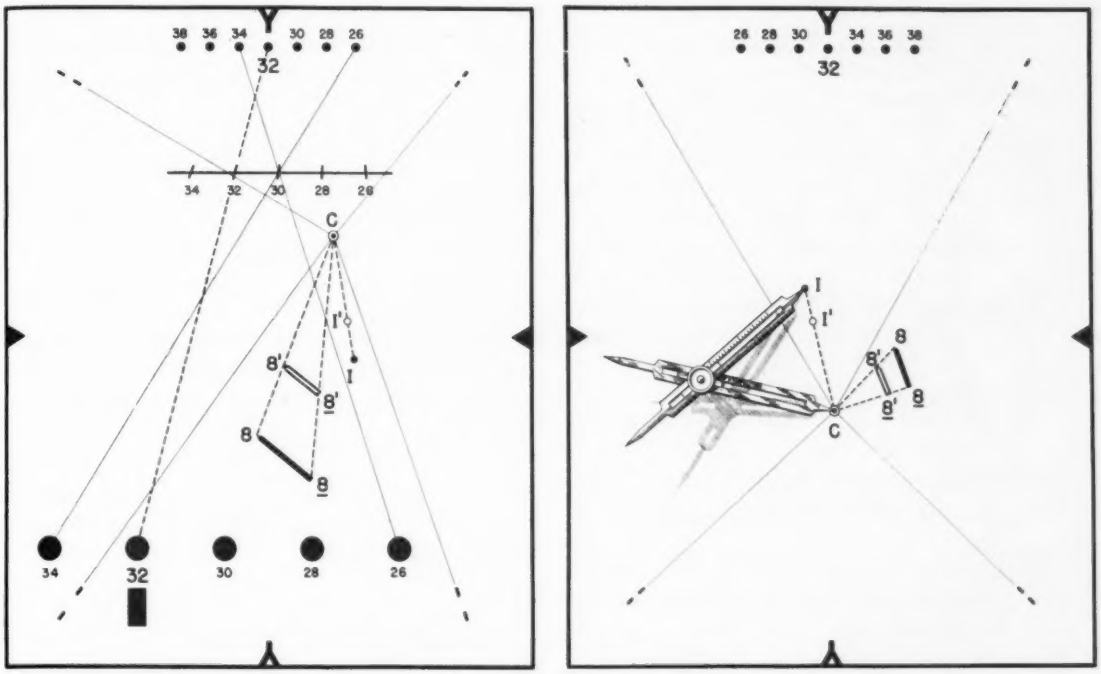

Fig. 9. Lateral and anteroposterior films of a needle (8-8) and critical point (*I*), showing construction of their orthographic projections (8′-8′ and *I*′). Lateral film is at left, anteroposterior film at right. The location of point *C* by extension of the director images is seen on both films. The true scale appears across the top of each film. The image of the height gauge is across the bottom of the lateral film. Construction between the image of the height gauge and the true scale creates the implant scale. Using this scale, the roentgen-ray images of points in the implant are measured to determine their true heights above the anteroposterior film. Their orthographic projections on the anteroposterior film are then located between their roentgen-ray images and point *C*, using a proportional divider to solve equation (3). Using the true scale on the anteroposterior film, the orthographic projections are measured to determine true distances from the lateral film. The lateral view is then corrected, using the proportional divider, as before.

done on a tracing table. As an example of the constructions, Figure 9 shows the correction of one needle (8-8) and one critical point (I), from the lateral and anteroposterior films of an actual case, to their orthographic projections (8′-8′ and *I*′).

1. Place the anteroposterior and lateral films side by side (lateral film to the left), making the *V*-*V* reference lines horizontal.
2. To locate point *C* on both films:
   (a) Draw and extend a straight line through the image of each pair of director pins.
   (b) Label the common intersection of these lines on each film with the letter *C*.
3. Label the sources:
   (a) Place a dot at the end points of each needle.
   (b) On the anteroposterior film assign a number to each needle, underlining the number at one end and not underlining it at the other.
   (c) Label the needles in the lateral view, assigning the same numbers and underlined numbers to corresponding ends.
4. Label the critical points:
   (a) If a critical point is visible on both films:
      (1) Assign a roman numeral to it.
      (2) Correct the anteroposterior and lateral images of it in exactly the same manner as the end points of the needles are corrected in steps 9 through 13.
   (b) If a critical point is not visible on the films, but has been designated as lying at specific distances from some visible reference point (such as the end of a

needle or a dead radon seed):

(1) Assign a roman numeral to the visible reference point.

(2) Correct the anteroposterior and lateral images of the reference point in exactly the same manner as the end points of the needles are corrected in steps 9 through 13.

(3) In the corrected anteroposterior and lateral views of the implant, measure off the specified distances from the corrected reference point in order to locate the required critical point.

(4) Assign a roman numeral to the critical point.

5. Label the true scale divisions on each film:
   (a) The division at the *Y* marker is labeled 32.
   (b) On the anteroposterior film, label the other marker with numbers increasing to the right in 2 cm. steps.
   (c) On the lateral film, label the other markers with numbers increasing to the left in 2 cm. steps.
6. Label the height gauge markers on the lateral film:
   (a) The accented division is labeled 32.
   (b) Label the other markers with numbers increasing to the left in 2 cm. steps.
7. Establish the location of the *implant scale* on the lateral film:
   (a) Draw a line from the highest visible marker of the image of the height gauge to the division on the true scale which has the same value as the lowest visible marker of the height gauge.
   (b) Draw a line from the lowest visible marker of the height gauge to the division on the true scale which has the same value as the highest visible marker of the height gauge.
   (c) At the crossing of these lines, draw a horizontal line. This will be the implant scale.
8. Establish the divisions on the implant scale:
   (a) Lay a straigt-edge on the lateral film connecting the 32 cm. division on the height gauge with the 32 cm. division on the true scale.
   (b) Make a mark where the straight-edge crosses the implant scale and label it 32.
   (c) Similarly, mark off other divisions on the implant scale.
9. On the lateral film, the true heights of the ends of the needles above the anteroposterior film can be found by reference to the implant scale. Record these distances.
10. Place a sheet of tracing paper over both films. Trace the true scale from the anteroposterior film and point *C* from both films.
11. Correct the anteroposterior image of the implant. For the end of each needle, proceed as follows:
   (a) Adjust a proportional divider (according to the manufacturer's instructions) to give this ratio of end openings:

$$\frac{\text{smaller end opening (designate as end } A)}{\text{larger end opening (designate as end } B)} = \frac{100-d}{100}$$

   where d is the distance of the implant point from the anteroposterior film, obtained in step 9.
   (b) Place a straight-edge between point *C* and the chosen point.
   (c) With end *B* of the proportional divider, span the distance from point *C* to the chosen point.
   (d) Invert the instrument and place one of the divider tips of end *A* on point *C*.
   (e) Set the other divider tip of end *A* on the line between point *C* and the point to be corrected. This locates the corrected position of the chosen point. Assign the same number to it, but add a prime mark.

   After correcting all the points in the anterposterior view, remove the anteroposterior film from under the tracing paper.
12. In the corrected anteroposterior view on the tracing paper, the true distances of the ends of the needles from the lateral film can be found by direct reference to the true scale. Record these distances.
13. Correct the lateral image of the implant:
   (a) Using the proportional divider as before, correct all the points in the lateral view, using the point to lateral film distances as obtained in step 12 for values of *d*.
   (b) Remove the lateral film from under the tracing paper.

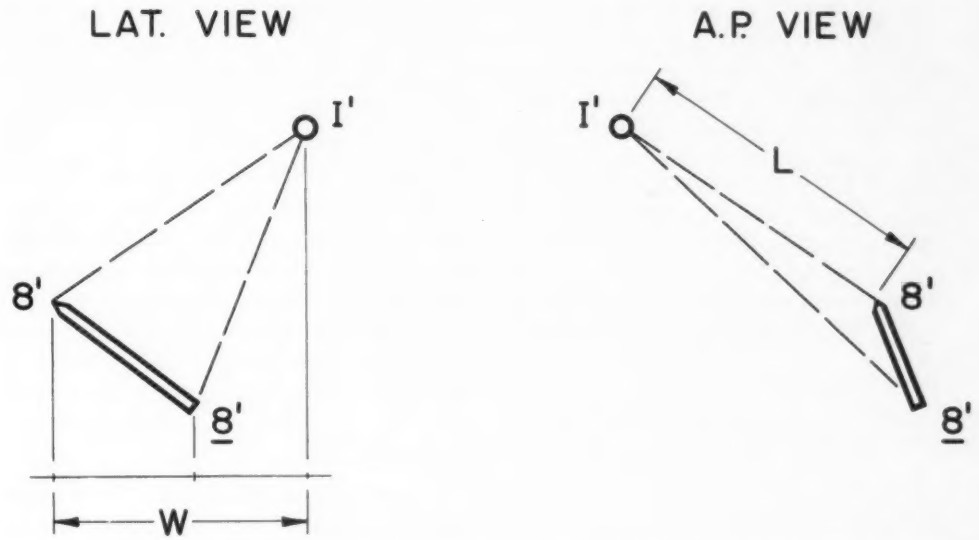

FIG. 10. Tracing of the orthographic projections of the needle and critical point from Figure 9. To find the true length of line $8'I'$, the dimension W is taken from the lateral view, and the dimension L is taken from the anteroposterior view.

GRAPHIC LOCALIZATION

For reference purposes, Figure 10 shows the corrected anteroposterior and lateral views of needle 8′-8′ and critical point I', as traced from Figure 9. The construction involved in localizing that needle with respect to the critical point is shown in Figure 11*A* and 11*B*.

1. Draw a horizontal base line below the corrected lateral view.
2. Through each corrected point, drop a perpendicular to this line.
3. Construct a true length diagram for finding the true distance from each point to each

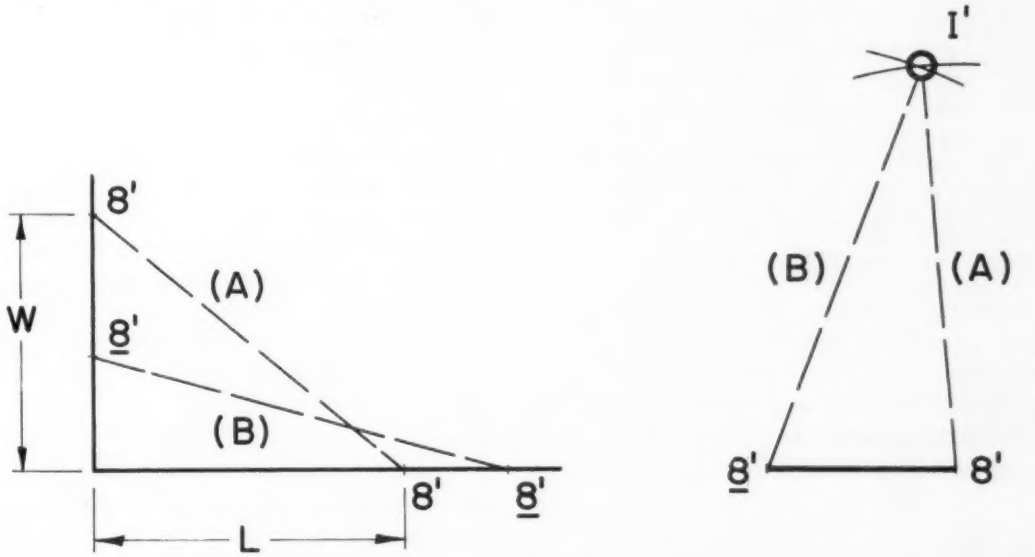

FIG. 11. (*A*) Construction of a true length diagram in which the true distance from 8′ to I' is the hypotenuse A, and the true distance from 8′ to I' is the hypotenuse B. (*B*) Localization of needle 8′-8′ with respect to critical point I'. By swinging the arcs A and B from the ends of a line drawn equal in length to the needle, the triangle formed by the needle and critical point is constructed in true size.

critical point. For a given critical point and needle proceed as follows:

(a) On a sheet of centimeter paper lay off on the vertical (or Y) axis the distance from each end of the needle to the critical point, as measured on the horizontal base line established in the lateral view in steps 1 and 2 above.

(b) On the horizontal (or X) axis lay off the distance from each end of the needle to the critical point, as measured directly in the anteroposterior view.

The true distance from each end point of the needle to the critical point is the hypotenuse of the right triangle whose sides are the X and Y distances for that point on the true length diagram.

4. Locate each needle with respect to each critical point. For a given critical point and source, proceed as follows:

(a) Elsewhere on the same sheet of graph paper containing the true length diagram, draw a horizontal line equal in length to the actual length of the radium needle.

(b) From one end of the line representing the needle, swing an arc equal in radius to the true distance from one end of that needle to the critical point, as taken from the true length diagram.

(c) From the other end of the line, swing a compass arc equal in radius to the true distance from the other end of the needle to the critical point.

The intersection of these arcs represents the true position of the critical point with respect to that needle.

DOSAGE RATE

Having localized all needles with respect to all critical points, dosage rates are calculated using the Quimby Tables.[1] The two distances required by these tables for each calculation are obtained directly from the graph paper, Figure 11*B*.

DISCUSSION

During the execution of actual cases, many shortcuts in the procedure will become apparent. In practice, it has been found that the dosage rates at three critical points from eight sources can be calculated in one and one half to two hours without the use of obvious short cuts. For example, doses delivered by relatively short sources at great distances have been calculated without resorting to the inverse square law. In a paper to appear in the future, several short cuts will be presented. These will demonstrate how the height gauge may be dispensed with and the use of the proportional dividers omitted. Alternate methods for the completion of the solution are possible once the orthographic construction has been obtained. Such a simplified solution might possibly be reduced to a monogram. The method is presented unabridged at this time, however, in order that others might find other simplifications by a fresh approach.

Many are interested in the introduction of suitable detectors into body cavities to determine by direct measurement the dosage rate from a radium implantation. The simple measurement of depth into a body cavity, however, is not sufficient information to locate accurately such probes, but they can be localized by the graphic method described.

One of the important problems which has become apparent and which is a poser in any method, is that of needle identification. Two methods are under consideration in our laboratory. One involves the coding of needles. The other is a stereographic method. Both require further development, but a satisfactory solution seems at hand. Until identification of sources is made practical, this method cannot be used in radon seed implantations, as it is too difficult to identify these sources on the anteroposterior and lateral films.

SUMMARY

A simple graphical construction converts the roentgen-ray images of radium sources to their orthographic projections, as they would be cast by parallel rays perpendicular to the film. Magnification and distortion is eliminated making possible accurate localization of the sources.

Special apparatus is needed in taking the roentgenograms. It is shown and described and is estimated to cost $200.00.

A complete clinical procedure for determination of radium dosage using this graphical method is presented, which includes roentgenography, selection of critical points and graphical localization in step by step working form.

The time required for localization of an implant of eight needles with three critical points is one and one half to two hours, with an error shown previously by Vreeland[2] to be less than 3 per cent.

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DISCUSSION OF PAPERS BY DR. BLOEDORN, MR. HOLT AND DRS. KLIGERMAN, VREELAND AND HAVINGA

Miss Elizabeth Focht, New York, New York. Unfortunately Dr. Herbert Parker was unable to be here today, and I was notified by Dr. Quimby that I had been appointed a volunteer to discuss these papers in his stead. I hedged, with the idea that one of the papers came from our own department and that therefore perhaps someone else ought to do the discussing; but here I am.

I am greatly interested in and pleased with the two papers that have just been given, and also with the paper of Dr. Kligerman and Dr. Vreeland last Sunday. After hearing these papers one has the impression that radium methods are definitely here to stay as long as irradiation is one of the methods of treatment. I say this because, if you will notice, all of the institutes from which these papers came are places which have access to the latest equipment, such as 1- and 2-million volt machines, telecobalt, betatron, or combinations thereof. Nevertheless, there is evidently enough interstitial and intracavitary work to make it worthwhile to spend a great deal of time and effort to analyze the patients and to compute the dosage more readily. It is evidently a method of choice in many cases, and the presentation of these papers is perhaps particularly suited to the American Radium Society.

Most of you are familiar with the Paterson-Parker system of radium dosage, in which the arithmetic has been worked out for different geometric arrangements of sources, in either single or double planes, cylinders, and so on, and the strength of the radium and the dose to be obtained are set forth in their rules. I hope you have been able to appreciate Dr. Bloedorn's paper today. I myself have read it and studied it rather carefully, and I believe one can get a much better appreciation of it that way than by hearing it in a few minutes' presentation.

I think it might also be considered a medical Part II to the original Paterson-Parker publication. This has actually been an excellently planned and systematic paper, and the physicist of course is delighted to see the radiologist have such an analytical grasp of the subject and be able to derive such practical use from a given system.

If all the implants look like the slides we have seen, and if all the calculations can be done by the radiologist by the Parker, Meredith and Stephenson method, then the physicist will have little to worry about further—as far as these radium implantations are concerned.

In regard to Mr. Holt's paper, I might tell you an illustrative story that I heard last evening. One of the residents went to a radiologist at Memorial Hospital and asked, "Can this wheel device be any good? It's so easy that I don't see how it can be right." I think this is one of its main points, namely, its ease of operation.

In this paper and in the other two—and, by the way, I am bringing in the Delafield paper from Sunday because I also heard a practice run on it in New York, and I think it is a very worthwhile paper, although I am not really expected to discuss it now—nevertheless, in all three of these papers, sort of gliding through the pages at times more or less in disguise perhaps, is our old friend the theorem of Pythagoras.

You all remember from high school days that the square of the hypotenuse is equal to the sum of the squares of the other two sides. Here the hypotenuse has reappeared as the distance wanted, either the distance from the point of interest to the center of the radium

tube or else the length of the radium needle, or again it came in as one of the dimensions of a given area.

Then, in a roentgenogram, one side appears magnified on the anteroposterior film, and on the lateral film of course is the other side. This magnification is corrected, and there are the two sides, from which one can get the hypotenuse by arithmetic, as in Dr. Bloedorn's paper, by construction as in Mr. Holt's wheel or by drawing it, as in Dr. Kligerman's and Dr. Vreeland's illustration.

If we were to make a comparison, the doses in the Paterson-Parker system apply to the implant as a whole, once the dimensions have been obtained. In the other methods the doses are gotten from each needle or tube in its relation to a given point.

The method developed by Dr. Kligerman and Dr. Vreeland is carefully worked out and I think it is the most accurate, especially close to the radium tube. The method of Mr. Holt when the distance is at least half active length of the radium and not too close to the ends is very simply done.

After all, radium tubes may differ considerably one from another, as was shown for instance in our institute when we used the scintillation counter and the automatic isodosimeter. We found there was a difference of several per cent from one tube to another, when they were supposed to have the same amount of radium and filter in them. Due to the difference in packing or the difference in filtration you can get larger errors, especially at the ends, than some of the errors that have been discussed in the three dimensional reproductions.

Considering this and also the fact that the selection of the anatomic position is subject of discussion and error, it would seem that this wheel method has a definite place in radium therapy. It has been a very good time-saver in our department, and the residents and fellows seem to look upon it very hopefully to solve some of their future problems.

We have heard three very good papers today and Sunday. I want to congratulate the authors and hope that their work will find the application in the future which I think it so well deserves.

A NEW RADIUM IMPLANT TECHNIQUE TO REDUCE OPERATING ROOM EXPOSURE AND INCREASE ACCURACY OF PLACEMENT

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THE radiotherapist or surgeon who implants radium needles is obliged to complete the procedure as rapidly as possible to avoid excessive exposure. A new technique has been developed at this hospital whereby the time of handling the radium is greatly diminished and the accuracy of implant greatly increased. Dummy needles in sheaths of plastic tubing are inserted and the dummy needles then replaced by radium.

The use of plastic tubing is relatively new in radiotherapy. Morton[1] devised a method for employing cobalt 60 in nylon threads. However, the use of plastic sheaths in connection with radium to reduce exposure has not, to our knowledge, been previously described.

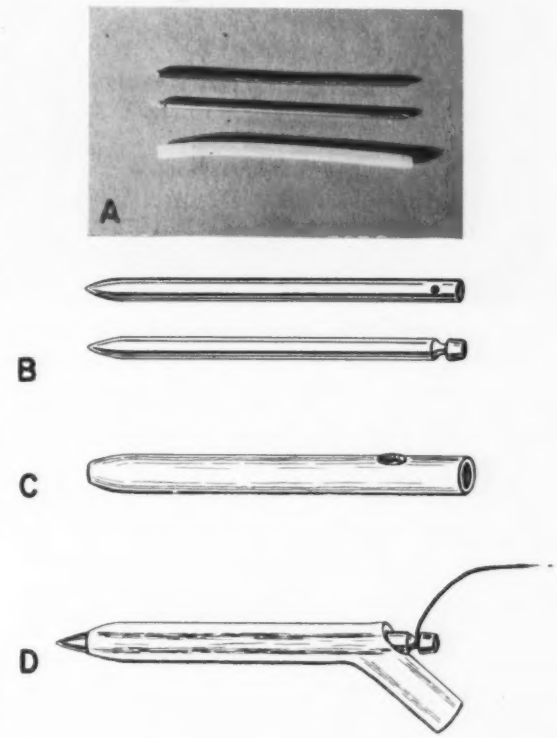

FIG. 1. (*A*) Photograph of radium needle (top), dummy needle and sheath. (*B*) Radium needle (upper) and dummy needle (lower) are of same dimensions. (*C*) Sheath is of polystyrene tubing with a lateral hole for insertion of needle. (*D*) Dummy needle in sheath. Note tab and white cotton thread.

PREPARATION OF MATERIAL

1. Stainless steel Kirschner wire of the diameter of the radium needles is cut into the same lengths as the needles. One end is pointed, and the other either eyed or grooved for a thread. The groove is satisfactory and simpler to make. The pieces of wire may be shaped with a file, either by hand or in a drill press (Fig. 1, *A* and *B*).

2. Thin-walled, inert plastic tubing is selected, such as that used for prolonged periods in blood vessels and other tissues, of proper inside diameter to receive the needles. It is cut to the same lengths as the needles to serve as sheaths. One end is beveled. Eight millimeters from the other end, a hole of the diameter of the needle is drilled through one wall (Fig. 1, *C*).

3. White cotton thread is tied around the groove of the dummy needle, which is inserted into the sheath through the lateral hole. The point extends outside the sheath, and the butt is at the hole. The length of tube beyond the hole (8 mm.) serves as a tab for handling (Fig. 1, *D*). For each radium needle to be used, there is on hand a dummy needle of the same dimensions inserted into a plastic sheath. If the sheaths are of polyethylene, they may be sterilized by autoclaving. For the polystyrene tubes employed in this study, chemical sterilization is necessary.

TECHNIQUE

For implantation, the dummy needle in its sheath is held with a clamp or with the fingers and inserted. The precise location is carefully checked and roentgenograms are taken after all the dummy needles are

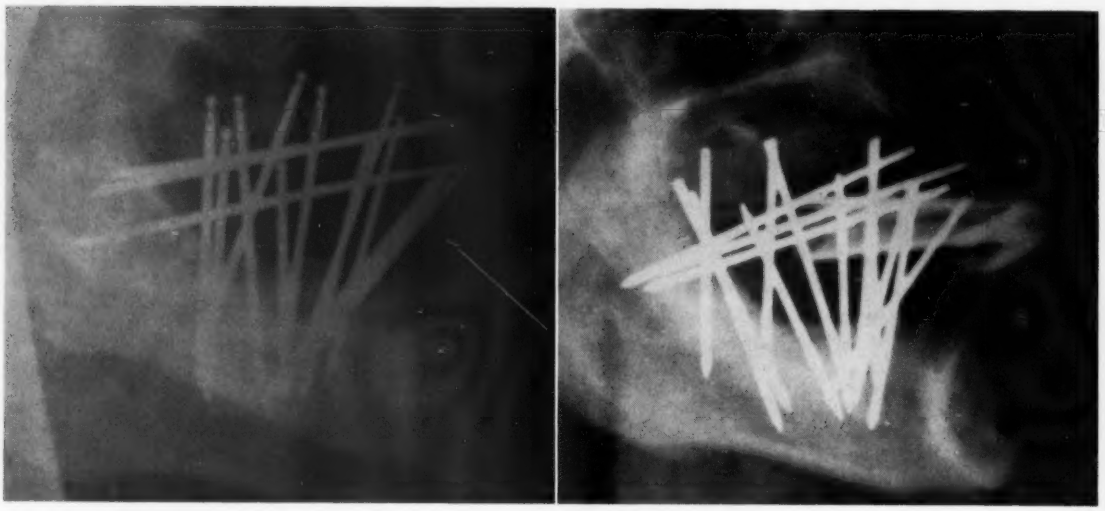

FIG. 2. Localization roentgenograms. Left film taken in operating room with dummy needles in place. Those marked with arrow were removed and reinserted. Right film taken with radium needles.

in place (Fig. 2). When corrections have been made and the dummy implant is considered satisfactory, the radium needles are brought into the room, after threading with suture needles fixed on black silk for contrast with the white cotton. Each dummy needle is rapidly replaced by its corresponding radium needle, which is sutured into the tissues. To keep the sheath from being removed with the dummy needle, the tab is held with a clamp. The tab and the suture prevent the sheath from becoming displaced.

The dose distribution is essentially the same as in conventional interstitial radium therapy, except that there is a decrease in the dose to the tissue closest to the sheath. This is due to the 0.5 mm. increased distance from the source of radiation, which is of no disadvantage, since the dose close to the source is generally excessive.

The method was employed first in cadavers and in a patient with carcinoma of the tongue and floor of the mouth. The dummy needles and sheaths were readily inserted. The sheath, when held in place by the tab, showed no tendency to come out with the dummy, which was easily replaced by the radium. The patient appeared to experience no greater discomfort or tissue reaction than expected from radium needles alone. There was no tendency for the needles and sheaths to become dislodged during the treatment, nor did the sheaths increase the difficulty of removal. Localization roentgenograms taken with the dummy needles in place revealed poor alignment of several anterior needles. This was readily corrected with no exposure (Fig. 2). The amount of exposure was found to be less than half that received by the same operators in previous radium insertions of the same order of complexity. As additional experience is gained in the use of this method, greater accuracy of implantation and speed of replacement of the dummy needles may be expected.

SUMMARY

A new method is presented for decreasing the exposure of personnel during radium implantation and achieving increased accuracy. Dummy needles in plastic sheaths are inserted, followed by rapid replacement of the dummy needles by radium.

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We wish to express our gratitude to our colleagues of the Department of Radiology for their suggestions and encouragement.

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Vol. 75, No. 3

AN INSTRUMENT FOR CALCULATING RADIUM DOSES

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IN CERTAIN roentgen therapeutic techniques using radium sources the following two conditions apply. First, the dose rates are required at a small number of specified positions, and secondly, the radium sources are sufficiently short in relation to their distances from these specified positions that they can be taken as point sources. Under these conditions the instrument described here (Fig. 1) allows routine calculations to be carried out simply and rapidly.

The particular application for which the instrument was developed is the assessment of doses given in the radium treatment of carcinoma of the cervix uteri and its use will be described in terms of this application, though the instrument could be used in any other application where the two conditions already stated apply.

The radium insertion follows a modified Manchester technique and consists normally of two ovoids, each containing one radium source and a central tube containing up to three radium sources. At this Institute the doses are calculated in full for each individual insertion at the conventional points *A* (left and right); points *O* (left and right) which are similar to the conventional points *B* but are defined in terms of distance from the bony pelvis; one or more points *R* in the rectum defined by suitable radiopaque markers; and sometimes points *F* on the surfaces of the ovoids. It is not the purpose of this paper to discuss the clinical aspects of the choice of these points which are developed from the conventional points *A* and *B* of Tod and Meredith,[1] but merely to note that the situation is that dose rates are required at

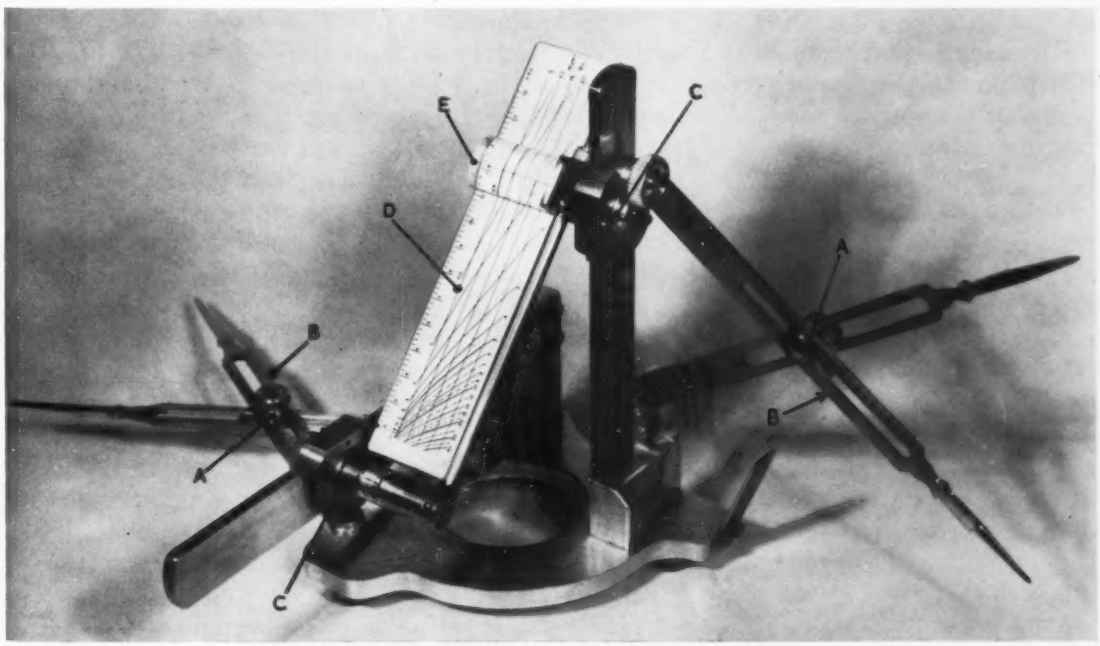

FIG. 1. General view of the instrument. *A—A*, sliding pivots of the proportional dividers; *B—B*, magnification scales; *C—C*, large sliding bearings (with clamping screws); *D*, dose rate scale; *E*, cursor for dose rate scale.

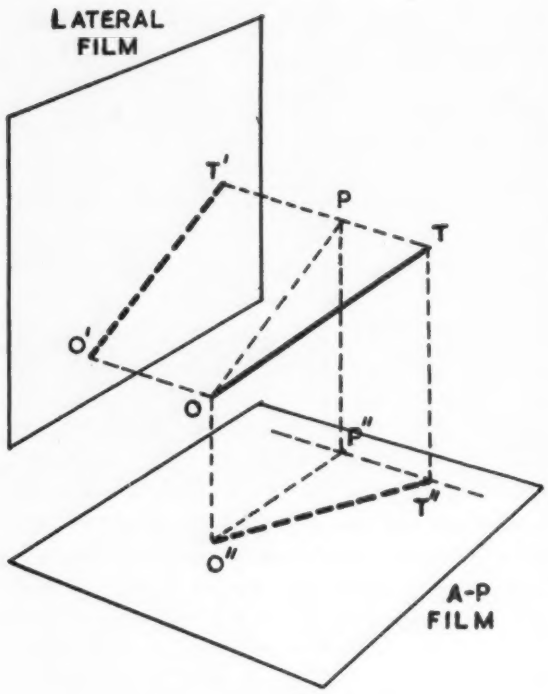

FIG. 2. Diagrammatic representation of the use of the instrument.

some five to eight points, these doses being delivered by from three to five radium sources.

The information required in the calculation is obtained by taking two roentgenograms of the insertion in the patient, one in the anteroposterior view and one in the lateral view. Special precautions are taken to ensure that the angle between the roentgen beams is exactly 90° and wire markers are placed on the diagnostic table to enable the magnification of each image to be determined.

On each of the processed roentgenograms the centers of the radium sources are marked in pencil, as are also the clinical points *A*, *O*, *F* and *R*. To illustrate the use of the instrument we will describe how the dose rate is found at the left point *O* from the top source (*T*) in the central tube. Figure 2 shows how the required dimensions are obtained. *O* is located in the patient's left pelvis, points *O'* and O'' are its images marked on the lateral and anteroposterior roentgenograms respectively. Similarly, *T* represents the center of the top radium source in the central tube and *T'* and *T''* its images on the two films. It is first required to find the true distance *OT*. In Figure 2 the distances *O'T'* and O''*T''* are the true distances after correcting for magnification. This is done by adjusting the sliding pivot points of the proportional dividers (shown in Figure 1) to line up to the required readings on the magnification scales. One pair of dividers is kept set for the magnification of the anteroposterior film and one pair for the magnification of the lateral film. Then when the points of the appropriate dividers are set on the images *O'* and *T'* on the lateral roentgenogram, the distance moved from its zero position by the large sliding bearing attached to the other end of the dividers is the correct length *O'T'*. A similar procedure is carried out on the anteroposterior film except that, as is clear from Figure 2, what is required is not *O''T''* but its projection *P''T''* on a line parallel to the central axis of the roentgen beam when taking the lateral roentgenogram. (It is actually the projection *P''T''* which is originally marked in pencil on some convenient line on the anteroposterior film.) The distance moved by the second large sliding bearing thus corresponds to the line length *P''T''*. The hypotenuse of the triangle formed by the two main slides and the dose-rate scale will then give the true distance *OT* as is clear by inspection of Figure 2 (where $OP = O'T'$ is the displacement along one slide, and $PT = P''T''$ is the displacement along the other). This scale forming the hypotenuse of the triangle is fixed by a pivot to one of the sliding bearings and slides under a cursor which is fixed by a pivot to the second bearing. The two main slides must be mutually perpendicular with the positions of zero displacement of the sliding bearings being on a common straight line.

If the scale is calibrated in centimeters it will record directly the true distance *OT* and it is possible that the instrument in this form might have uses in such applica-

tions as pelvimetry. For known strengths of radium sources the dose rates at various distances can be calculated from the inverse square law and the scale can be calibrated directly in terms of dose rates in roentgens per hour. On this instrument this has been done for sources of 5, 10, 15, 20 and 25 mg. of radium screened by 1 mm. of platinum since these are the sources used for this particular clinical application. The actual form of the scale shown in the illustration is merely a convenient way of marking in a small space a large number of divisions on five scales connected by constant multiplying factors.

Due to mechanical limitations both sliding bearings cannot be at zero together and in practice this has been made use of to limit the smallest reading on the scale to 2 cm. since at distances shorter than this the radium tubes used cannot be taken as point sources without introducing too great an inaccuracy. (When dose rates are required at distances less than 2 cm. from a source these are read from isodose curves drawn for that particular source's length.)

Following the steps outlined above the instrument allows the dose rates at all the specified points to be found quite quickly, the only arithmetic required being the simple addition of the contributions from the separate radium sources at each of the clinical points. When the instrument is well constructed the accuracy achieved is certainly better than that with which the original sources and clinical points can be marked on the roentgenograms.

Radium Institute
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A NEW TYPE OF HYSTEROSTAT

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THE radium applicator for treatment of cancer of the corpus uteri presented here is designed to give a predetermined distribution and intensity of radiation by the use of an instrument easily inserted and conforming to the triangular shape of the uterine cavity.

We have designed a folding radium applicator of brass that can be introduced through the dilated cervical canal like a closed umbrella and opened within the uterus to fit against the sides and fornices in the shape of a triangle. It consists of three hollow sections, each articulating by a hinge, and is manipulated by means of the two slender handles to perform like a "monkey-on-a-stick." The handles have a flange guide to keep the articulation within one plane of action (Fig. 1, 2 and 3).

The applicators in use are of two sizes, one for the smaller senile uterus. Either will hold a total of nine 10 mg. needles, assuring radiation from a 90 mg. triangular source. The geometric pattern of radiation approaches the Paterson and Parker system and covers a uniform field. The isodose curves would approximate the anatomic shape of the uterus.

The specimen shown in Figure 4, cut open to reveal the hysterostat, had been irradiated one month previously with 4,500 mg. hr. through this applicator. The dark areas indicate beginning necrosis adjacent to the radium.

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FIG. 1. Applicator disarticulated for loading.

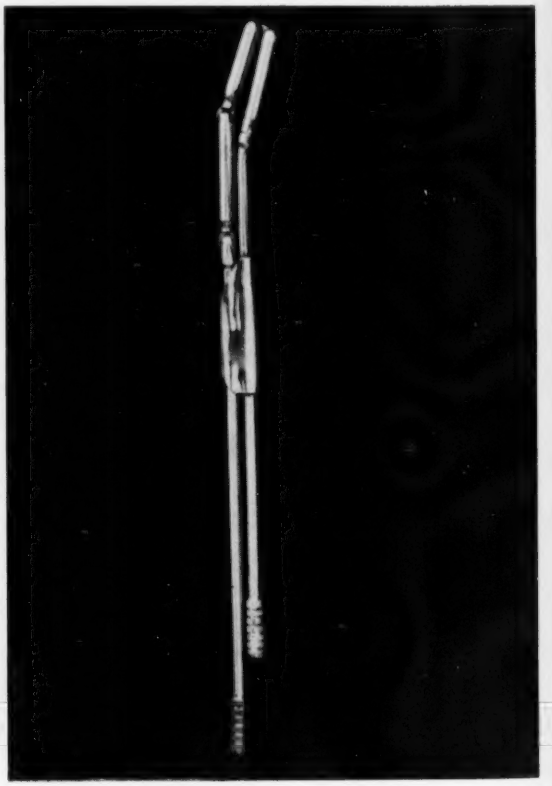

FIG. 2. Applicator in collapsed position for passing uterus.

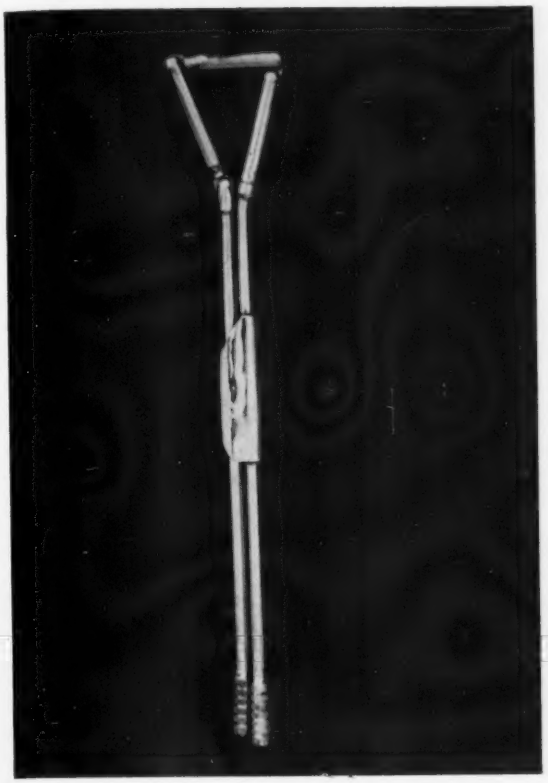

Fig. 3. Applicator in extended open position.

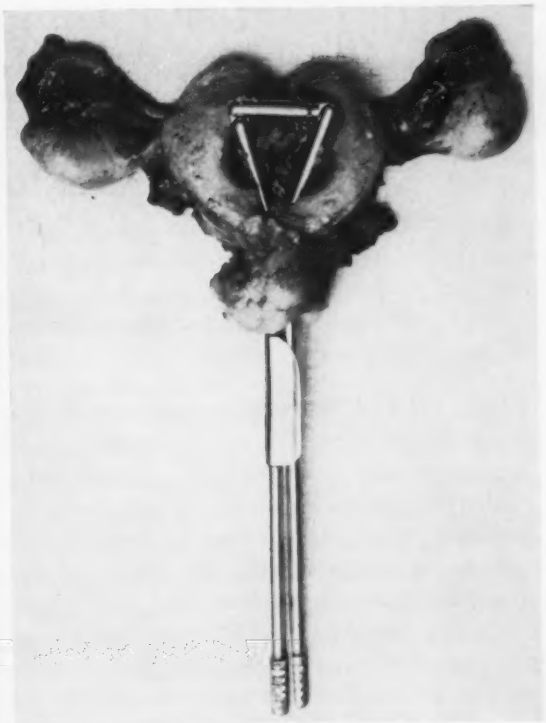

Fig. 4. Uterus specimen opened to show applicator *in situ*.

THE INTENSIVE DIVIDED-DOSE IRRADIATION THERAPY OF CARCINOMA OF THE UTERINE CERVIX: RATIONALE AND LATE RESULTS*

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IRRADIATION therapy has been in use at the Mayo Clinic in the treatment of cancer of the uterine cervix since 1915. Many modifications of the method have occurred until it has reached its present status, but the underlying principles of the radium therapy have remained unchanged since the early days. The technique, as of the present time, will be described as well as the principles of treatment. Then the advantages and disadvantages of the system will be discussed and, finally, the late results.

DESCRIPTION OF TECHNIQUE

A complete course of treatment for cancer of the cervix, carried out whenever cure seems possible, covers a period of about four weeks. Thorough general and pelvic examinations yield essential information regarding the physical status of the patient and the stage or extent of the cancer according to the International classification (previously League of Nations classification). Biopsy of the growth tells us the type of cell and the microscopic grade of the lesion, knowledge not as important for prognosis as the stage. In cases of cancer of Stage III or IV, excretory urograms are carried out to be certain that the kidneys are functioning normally.

Treatment is started with radium therapy, and roentgen therapy is instituted within one or two days and continued concurrently with the radium therapy. The unit of radium treatment is the 50 mg. tube, filtered with 1 mm. of platinum. The active length of the tube is 11.7 mm. The over-all length is 19 mm. and the diameter is 4.0 mm. Dilatation of the cervix, which could press cancer cells out into the circulation, is avoided. Trauma is avoided and good exposure of the lesion is obtained by having the patient assume the knee-chest position at every radium treatment; resultant expansion of the vagina with air affords space for abundant gauze packing following insertion of the radium tube.

Radium treatments are given twice weekly for a period of four weeks. In the absence of complications, such as infection or hemorrhage, hospitalization is necessary only on the day and night of the radium treatments. In the two or three-day interval between radium applications, the patient is ambulatory. Being out of the hospital and up and around have been found to maintain the strength and morale of the patient.

With radium treatments, the effort is made to obtain a homogeneous irradiation along the entire birth canal. The 50 mg., platinum-filtered tube is introduced into the proximal portion of the cervical canal for a period of ten to fourteen hours at each of the first two treatments, the posterior vaginal wall being packed well away from the radium to secure protection of the rectum. In the third and fourth treatments, also of ten to fourteen hours each, the tube is placed in the middle or deeper part of the cervical canal.

* Read at the Fifth Inter-American Congress of Radiology, Washington, D. C., April 24 to 29, 1955.
† The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

Since a cervical cancer frequently spreads through the internal os to involve the endometrium, at the fifth radium treatment a tandem is introduced into the uterine cavity, two 50 mg. tubes being used for a period of twenty to twenty-four hours. Roentgen therapy is necessarily omitted on this day. The last three treatments are given in the vaginal cavity, the 50 mg. tube being enclosed in a plastic cylinder of appropriate size, but the cylinder most frequently used has a wall thickness of 1 cm. and is placed transversely across the face of the cervix, then in the right vaginal fornix, and finally in the left vaginal fornix, for a treatment time of ten to fourteen hours each.

Thus, a complete course of treatment for a small lesion in a patient with a small vaginal cavity would total around 5,500 mg. hours in four weeks; a bulky carcinoma would receive a minimum of 7,300 mg. hours. Point *A* would receive at least 7,000 gamma roentgens and point *B* would receive at least 2,000 gamma roentgens, in a large tumor with full dosage.

The roentgen therapy is administered to two anterior and two posterior pelvic ports with midline protection between adjacent areas. Daily treatments of 200 r (air) are delivered at 70 cm. distance to each of two ports for a total dose of 2,000 to 2,200 r per port, employing 250 kv. (peak) radiation with half-value layer of 1.3 mm. copper. Since the advent of cobalt teletherapy, many patients are now being treated with this agent. However, all of the patients with whom this report is concerned were treated during the period 1940 to 1948 inclusive, and the technique of roentgen therapy was considerably different. Treatment was administered immediately after completion of the course of radium therapy. Two anterior and two posterior pelvic ports were treated, each of which measured approximately 15 by 15 cm., and there was no midline separation between adjacent fields. A total dose of 540 r (air) was administered to a single field daily employing 200 kv. (peak) with half-value layer of 1.0 mm. copper, and the entire course of treatment was completed in four days. This course of treatment was repeated after an interval of three months.

Following treatment, patients are examined every three months during the first year, with careful pelvic examination and also inspection of the part with biopsy of any apparently unhealed tissue. If satisfactory healing has occurred at the time of these examinations, they are repeated twice a year during the second year following treatment, and once a year thereafter. In recent years, Wertheim hysterectomy plus removal of accessible pelvic lymph nodes has been performed in a selected group at the first revisit three months after treatment. This procedure has been restricted generally to younger patients with Stage I or Stage II lesions who present good operative risks, and the method is still on a trial basis.

PRINCIPLES OF THIS TECHNIQUE

This method of treatment relies more on radium therapy than several other techniques; the radium applications take care of the entire uterus, and roentgen therapy is relied on to supplement the radium in an effort to sterilize any spread of cancer into the lateral pelvic lymph nodes. The main principles of this method are homogeneous irradiation along the entire birth canal, intensive treatment over a period of four weeks, no dilatation of the cervix beyond that caused by the placement of the 4.0 mm. wide radium tube, and avoidance of trauma. The knee-chest position affords the best exposure and facilitates gentle placing of the applicators. It also provides room to insert adequate packing to protect the bowel and other normal structures from destructive effects of radiation.

ADVANTAGES

This method of treating with radium twice a week over a period of four weeks permits evaluation of early effects, so that treatment can be hastened or delayed if necessary. Nitromersol (metaphen) solu-

tion is used to cleanse the surface of the cervix, and when the radium tube is in place one of the sulfonamide powders is sprayed over the field. If infection spreads, treatment can be delayed and antibiotics used until the patient's temperature returns to normal. Hemorrhage can be controlled by tight gauze packing inserted while the patient is in the knee-chest position. The main complications of infection and hemorrhage can usually be well controlled.

The small, 50 mg., platinum-filtered tube is a remarkably adaptable agent for treatment. Many rigid applicators have been used successfully by radiologists, but most require dilatation of the cervix and a normal-sized vaginal cavity. Many of our patients present advanced lesions often filling the vaginal cavity and obscuring the normal landmarks. After one or two applications of the radium tube into the mass of cancer, shrinkage occurs so that the cervical canal can be located and treatments continued.

By separating the radium treatments and permitting the patients to be ambulatory and out of the hospital between applications, the morale and strength of each patient are improved. Treatments are painless and require no anesthesia; a hypodermic of morphine is usually given only before the intra-uterine application.

DISADVANTAGE

The main disadvantage of the method is a scarcity of hospital beds at short notice in many treatment centers. We have always been fortunate in having adequate hospital facilities, so that treatments seldom have to be delayed for lack of hospital beds when needed.

RESULTS OF TREATMENT

In 1948 the late results of radium therapy at the Mayo Clinic for cancer of the cervix were published.[1] The study included all patients treated with irradiation in the years 1915 to 1939 inclusive. Of 1,581 patients traced, 519 (32.8 per cent) survived five or more years. The patients traced were 88 per cent of the total number treated over these years, 1,799 in all. The absolute cure rate through 1939 was 28.8 per cent, counting all untraced patients as dead of cancer. Radiation therapy was the type of treatment in 59.2 per cent of the 3,798 patients during the years through 1944. Eleven and seven-tenths per cent of the patients were treated by operation alone, excluding exploratory operations. Smaller groups had limited treatment of radium alone or roentgen rays alone for palliation, or else combinations of surgical and radiation therapy. Relative five-year survivals after surgical treatment alone were 29.1 per cent.

The reasons for the relatively low cure rate in patients treated with radium were twofold. Up to recent years irradiation has not been the treatment of choice for early favorable lesions. Only 15 per cent of the total treated by radiation were of Stages I and II, whereas in the present study 30 per cent of the total received irradiation. Secondly, extremely poor results attended the early years, when knowledge of the proper use of radium was being acquired. In the first five-year period, 1915 through 1919, for instance, the five-year survival rate of traced patients was only 8.9 per cent. Five-

TABLE I

MALIGNANT LESIONS OF THE CERVIX
1940 TO 1948 INCLUSIVE
STAGE OF INVOLVEMENT

	Cases	
	Number	Per cent
Squamous cell epithelioma		
Stage		
0	96	7.3
I	122	9.3
II	299	22.8
III	341	26.1
IV	147	11.2
Other malignant lesions of cervix	116	8.9
Modified	188	14.4
Total	1,309	100.0

TABLE II

MALIGNANT LESIONS OF THE CERVIX
1940 TO 1948 INCLUSIVE
TYPE OF TREATMENT

Treatment	Cases	
	Number	Per cent
Radium therapy alone	132	10.1
Roentgen therapy alone	46	3.5
Radium and roentgen therapy	831	63.4
Surgical therapy alone	139	10.6
Surgical and radium therapy	19	1.5
Surgical and roentgen therapy	47	3.6
Surgical, radium and roentgen therapy	95	7.3
Total	1,309	100.0

TABLE III

SQUAMOUS CELL EPITHELIOMA OF THE CERVIX
TREATED BY RADIATION THERAPY
1940 TO 1948 INCLUSIVE
FIVE-YEAR SURVIVAL RATES ACCORDING TO
GRADE OF MALIGNANCY (BRODERS)

Grade	Patients		Five-year Survival	
	Total	Traced	Number	Per cent*
1	0	0	0	
2	76	69	48	69.6
3	445	405	243	60.0
4	273	254	136	53.5
Total	794	728	427	58.7

* Based on traced patients. Inquiry as of January 1, 1954.

year survivals in later five-year periods among traced patients have been 40 per cent or more.

In the years covered, the mortality rate of this treatment was 0.2 per cent, so that this system of treatment seems well tolerated with little serious risk.

The report published in 1948 summarizes the five-year survival rate of patients treated in 1939 and earlier. The present study carries on the end results of treatments given in 1940 to 1948 inclusive.

TABLE IV

MALIGNANT LESIONS OF THE CERVIX
1940 TO 1948 INCLUSIVE
FIVE-YEAR SURVIVAL RATES FOLLOWING COMPLETE OR LIMITED RADIATION THERAPY

	Complete Therapy				Limited Therapy			
	Patients		Lived five or more years following radiation therapy		Patients		Lived five or more years following radiation therapy	
	Total	Traced	Number	Per cent*	Total	Traced	Number	Per cent*
Squamous cell epithelioma Stage								
0	(1)†	(1)	(1)	—	(1)	0	0	—
I	27	21	20	95.2	4	3	2	66.7
II	261	234	181	77.4	21	19	13	68.4
III	296	280	156	55.7	38	34	18	52.9
IV	84	80	27	33.8	61	56	9	16.1
Other malignant lesions of the cervix	50	50	24	48.0	39	33	4	12.1
Modified	35	30	14	46.7	141	123	29	23.6
Total	754	696	423	60.8	305	268	75	28.0

* Based on traced patients. Inquiry as of January 1, 1954.
† Per cents are not calculated for numbers in parentheses.

TABLE V

MALIGNANT LESIONS OF THE CERVIX TREATED BY RADIATION THERAPY
1940 TO 1948 INCLUSIVE
FIVE-YEAR SURVIVAL RATES ACCORDING TO STAGE OF LESION

	Patients		Five-year Survival	
	Total	Traced	Number	Per cent of traced patients*
Squamous cell epithelioma Stage				
0	(2) †	(1)	(1)	—
I	31	24	22	91.7
II	282	253	194	76.7
III	334	314	174	55.4
IV	145	136	36	26.5
Other malignant lesions of cervix	89	83	28	33.7
Modified	176	153	43	28.1
Total	1,059	964	498	51.7

* Based on traced patients. Inquiry as of January 1, 1954.
† Per cents are not calculated for numbers in parentheses.

Table I indicates the total number of malignant lesions of the cervix treated by all methods at the clinic from 1940 to 1948 inclusive. Pathologically, squamous cell carcinoma comprises approximately 91 per cent of cervical malignant lesions. The other malignant lesions of the cervix mentioned include chiefly adenocarcinomas, although some adeno-acanthomas and one hemangio-endothelioma were found. The group of modified cases includes all those in which radiation or surgical therapy for the carcinoma had been received elsewhere prior to the treatment received at the clinic. It is, of course, often impossible to stage such lesions accurately. An attempt to do this was always made for the sake of our own comparative observation. The total group observed in this nine-year period comprised 1,309 cases of malignant lesions of the cervix.

Table II shows the different forms and combinations of therapy utilized in the series. Definitive radiation therapy alone was given to 1,059 patients; that is, 1,009 patients shown in the first three items of Table II plus 50 patients who had complete radiation treatment and months later underwent operation (Wertheim hysterectomy). Surgical and radiation therapy were combined in 161 patients. In the vast majority the radiation therapy in this group consisted of postoperative administration for prophylactic reasons.

Table III gives the survival rate according to grade of malignancy for squamous cell epithelioma. As in the previous series, the grading is carried out according to Broders' classification. From the figures shown there would seem to be some slight influence of the grade of the lesion on survival; but, as has been previously shown, there is no such close correlation as with the stage of the lesion.

Table IV divides the series into the groups receiving complete radiation therapy, as described previously, and those receiving limited radiation therapy. Only 2 patients having so-called *in situ* squamous cell epithelioma of the cervix were treated by radiation therapy. Both of these patients refused surgical treatment. The chief reasons for limited therapy are (1) pelvic cellulitis, (2) hemorrhage and (3) profound debility. The first cause has been almost entirely obviated since antibiotics have come into general use, but in the early years of this series, few such adjuncts were available.

Table V shows the survival statistics of all patients treated by radiation therapy. Of the 1,059 patients treated, 964 (91.0 per cent) have been satisfactorily traced. Further investigation is being made at the present time to determine the status of the patients not yet traced. The present report deals with only one phase of the treatment of cervical cancer at the clinic and subsequent papers by the authors will amplify the foregoing results. The over-all five-year survival rate of 51.7 per cent on all traced patients treated with radiation ther-

apy shows a gratifying increase over the 32.8 per cent survival rate in the previously reported group. If all untraced patients are considered dead of cancer, the absolute survival rate in the present series is 47.0 per cent.

SUMMARY

The technique of treatment of carcinoma of the uterine cervix in use at the present time at the Mayo Clinic has been described, and results have been tabulated, along with a discussion of the general principles, advantages and disadvantages of the method. Slight changes in radium technique have evolved from year to year, but the general principles of treatment have not been altered since the commencement of radium therapy at the clinic in 1915. However, rather marked changes have been made in the technique for roentgen therapy, particularly during recent years. Results obtained in the years 1940 through 1948 inclusive (51.7 per cent of traced patients surviving five years) are better than those reported in the past. The five-year results offer a good indication of "cure" in cancer of the cervix; previous studies have shown that 80 per cent of recurrences occur within the first two years, while less than 4 per cent are found after five years from completion of therapy of the primary growth.[2] The superior five-year results in the present study compared with results affecting patients treated in 1915 to 1939 inclusive are probably due in part to minor improvements in technique and in part to earlier diagnosis and treatment. The interest of the public in cancer, because of the publicity given this dread disease, has shown patients that cancer is curable in early stages, and has been instrumental in providing opportunity for earlier diagnosis and treatment.

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TREATMENT OF ENDOMETRIAL ADENOCARCINOMA*

A STUDY OF 381 CASES AT THE NEW YORK HOSPITAL

A PRELIMINARY REPORT

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THERE are two schools of thought regarding the management of patients in whom a diagnosis of endometrial cancer has been established. One group advocates more or less routine application of intracavitary radium followed by major surgery; the other proceeds first with the operation and then employs postoperative irradiation whenever indicated. The latter method of therapy has been employed at the New York Hospital for many years.

Arneson,[1] Schmitz and his co-workers,[11] and others who advocate preoperative radium claim a higher cure rate and a lower incidence of vaginal metastases. Peightal[10] and the authors prefer the surgical treatment followed by postoperative irradiation and report a comparable cure rate. They regard the vaginal "recurrences" as actual metastases that would have occurred anyway, irrespective of the order of treatment.

PRESENT STUDY

The present study embraces a time period from September 1, 1932, to December 31, 1954, during which time 541 cases were discharged with the diagnosis of endometrial adenocarcinoma, according to the Annual Reports of the Hospital. A number of these patients had been admitted several times for the treatment of either the cancer or the metastases or so-called "recurrences." However, for the purposes of this study, data obtained on repeated admissions were considered in terms of the given patient, so that each case was counted only once. Therefore, the actual total number is 381, which forms the basis for this report.

STUDY WITHIN A STUDY

Toward the end of 1946, the late Dr. Stander gave the authors permission to make a study on clinic or ward patients of the surgical pathology of endometrial cancer, including the spread of benign and malignant endometrium to the lymph nodes. The object was to determine the pathologic status at the time the patient was first seen in the office. Heretofore most clinicians have relied on autopsy data which usually represent an advanced stage of the disease. This study program was initiated on January 1, 1947, and was to continue for ten years or until 1957. This plan has continued despite the untimely death of Dr. Stander, under the guidance of R. Gordon Douglas who plans to re-evaluate the entire program of treatment in 1957 and thereafter make the indicated changes if any. The first private patient to have pelvic lymphadenectomy for endometrial cancer was operated upon by Dr. Frank Smith in 1947. This patient had positive lymph nodes and is the only such case still alive five years or more. Her survival has been eight years. Recently there has been an increasing number of private as well as ward cases that have had some form of lymphadenectomy.

During the course of this study several reports have been published. The first article, by Javert and Hofammann[7] in 1952, presented the surgical pathologic observations of 280 cases. This article

* From the Department of Obstetrics and Gynecology, Cornell University Medical College and the Woman's Clinic of the New York Hospital. Presented at the Thirty-seventh Annual Meeting of the American Radium Society, Washington, D. C., April 21–23, 1955.

TABLE I

CLINICAL CLASSIFICATION OF ENDOMETRIAL CANCER

		No.	Per cent
Stage I	Adenoma malignum, normal to small uterus, etc.	318	83.5
Stage II	Parametrial thickening, enlarged uterus, etc.	23	6.0
Stage III	As above plus adnexal spread, peritoneal implants, etc.	12	3.1
Stage IV	Distant metastases	20	5.2
Miscellaneous—Unsuspected, discovered in specimen. Usually Stage O		8	2.1
Total		381	99.9

emphasized the lymphatic spread of endometrial cancer to the pelvic lymph nodes and also proposed a surgical pathologic classification that recognized such spread. This classification is based on sound pathologic principles and disregards the clinical estimation of the size of the uterus for reasons stated below. It provides for the determination of prognosis by the time honored surgical method of positive and negative lymph nodes. The second report[8] was made on the spread of benign and malignant endometrium in the lymphatic system. These surgical pathologic studies not only revealed the tendency of endometrial cancer to spread to the regional lymph nodes, a view contrary to the generally accepted opinions of the late 1940's but also pointed up the frequency of hematogenous spread, especially when the lymph nodes were positive. Endometrial cancer ranks with cancers of the prostate, bladder, kidney and colon as having a predilection to hematogenous dissemination and present methods of surgical and radiation therapy do not consider this aspect of the problem at all. What is needed is some substance that can be administered intravenously to destroy these metastases.

TABLE II

DIVISION OF CASES AS TO OPERABILITY

Operable (hysterectomy)	339
Not operated, inoperable, exploratory laparotomy[6]	42
Total	381

The present report is the third of this series and the first to evaluate treatment in terms of this classification. Once the surgical pathology has been established, it is foolhardy to evaluate results on the basis of clinical classifications. Most clinical classifications are valuable in that they serve as a basis for individualization and selection of the cases for the various programs of therapy. They also enable the operator to select patients as to operability. Such a classification is presented in Table

TABLE III

MANAGEMENT OF ENDOMETRIAL CANCER AT NEW YORK HOSPITAL

Surgery Alone		161
Surgery Plus Irradiation		178
Surgery, postoperative roentgen therapy	140	
Surgery, preoperative radium	27	
Surgery, postoperative roentgen therapy and preoperative radium	5	
Surgery, postoperative radium	3	
Surgery, preoperative radium and roentgen therapy	2	
Surgery, preoperative roentgen therapy	1	
Irradiation Alone		26
Radium only	15	
Radium and roentgen therapy only	8	
Roentgen therapy only	3	
No Therapy		16
No therapy (autopsy)	10	
Surgery refused	6	
Grand Total		381

TABLE IV

DISTRIBUTION OF CASES ACCORDING TO SURGICAL-PATHOLOGIC CLASSIFICATION[7]

		No.	Per cent
Stage O	Primary lesion limited to the endometrium	35	10.1
Stage I	Myometrial invasion only	225	65.2
Stage II	Direct extension to adjacent organs	51	14.8
Stage III	Lymph node metastases*	16	4.6 (20.0)
Stage IV	Carcinomatosis and hematogenous spread†	18	5.2
		345	99.9

* Incomplete data on 80 cases with lymphadenectomy.
† Two of these cases had positive nodes at laparotomy.

TABLE V

INCIDENCE OF STAGE O CASES

Year	Total No. of Cases	Stage O	
		Number	Per cent
1932–1946 (14 years)	178	5	2.8
1947–1954 (8 years)	203	30	14.8
Total	381	35	9.2

1. It includes 21 cases which were autopsied.

The passing years have seen a change in the total number of cases considered operable, because of earlier diagnosis, better operative techniques and better management of the medical complications. The cases have been divided as to operability in Table II.

The type of treatment is summarized in Table III. It can be seen that the patients have been individualized and that various methods of treatment have been employed. Surgery, either alone or followed by definitive, rational postoperative therapy designed to prevent or reduce the clinical incidence of "recurrence," has been the procedure of choice at the New York Hospital.

Table IV reveals the distribution of cases according to data obtained clinically, by abdominal surgery and by surgical-pathologic study of the specimen, as described elsewhere.[7] Cases not treated surgically and coming to autopsy were excluded from Table IV. They have been included in Table I, referred to above. Comparison of the two tables reveals the differences between the pathologic and the clinical classification, chiefly in Stage 0, I and Stage III categories.

Prior to 1947 only 5 cases were found in which the disease was known to be

TABLE VI

AVERAGE WEIGHT OF 100 SURGICAL SPECIMENS OF UTERI CONTAINING ENDOMETRIAL CANCER

Description	No. of Cases	Average Weight, Grams	Range	Per Cent
Normal Size	18	96	90–100	46
Atrophic	28	68	40– 85	
Hypertrophy due to cancer	8	225	150–600	10
Hypertrophy, benign	2			
Myoma uteri plus cancer	24	363	130–1200	24
Adenomyosis plus cancer	20	153	105–260	20
Total	100			100

limited to the endometrium. Since that time 30 more cases have been so diagnosed as revealed in Table v, which reveals Stage 0 cases to be on the increase. This is probably due to the fact that the Papanicolaou vaginal and endometrial smears are widely used in the New York City area, from which the hospital obtains most of its patients. Table IV contains 6 more than the 339 operable cases in Table II because of data obtained by exploratory laparotomy.

Since 1947 it has been our policy to open each uterus in the operating room in order to inspect the endometrium. Each surgical specimen has also been weighed since that year in order to determine whether size was a useful criterion for the classification of these cases. Accordingly, the average weights of the last 100 cases have been summarized in Table VI, which shows that size is of little value since most of the uteri were either normal or atrophic or contained adenomyosis or myomata, so that in only 10 per cent could the enlargement be attributed to the cancer.

Selective or complete pelvic lymphadenectomy became part of the total hysterectomy procedure in 1947, for purposes of investigation. To date it has been performed on 80 patients, as shown in Table VII. It can be seen that 16 patients or 20 per cent had positive lymph nodes. Autopsies on 21 cases revealed positive lymph nodes in 16 other cases. All of these patients received postoperative irradiation. Only one has lived over five years, the case of Dr. Smith. Positive cases having the selective or incomplete removal of the lymph nodes were not re-operated, reliance being placed on the external abdominal irradiation. Brunschwig and Murphy[2] performed radical hysterectomy and pelvic lymphadenectomy on 57 cases and found positive lymph nodes in 10 or 17.5 per cent.

The known metastases, or clinical "recurrence" of endometrial cancer have been divided into two groups in Table VIII: Group I consists of 42 cases in which metastases existed at the time of the initial diagnosis of endometrial cancer before definitive therapy; Group II consists of 339 cases in which panhysterectomy had been followed by vaginal metastases (recurrence). It can be seen that vaginal metastases were observed in 40 or 10.5 per cent of the 381 cases. These usually occurred between two to two and one half years after operation, too late for "implantation" metastases. One case developed such recurrence five years after hysterectomy, another eleven years after hysterectomy. These metastases are also presented in Table IX according to the type of therapy employed. The highest incidences occur in those cases which received preoperative radium either alone or followed by surgery. The panhysterectomy operation did not increase the incidence of vaginal metastases. This evidence refutes those who advocate preoperative irradiation followed by hysterectomy in order to reduce the incidence of vaginal vault recurrence.

Observations referred to below confirm those of Way,[13] who found a higher incidence of vaginal metastases with the adenoacanthoma type of endometrial cancer. The authors regard these as representing hematogenous metastases. Accordingly all of the cases shown in Table I were regrouped according to Ewing's histologic classification and these data are seen in Table X.

The vaginal metastases were then studied in terms of the histologic type as indicated in Table XI. They were also studied in

TABLE VII

PELVIC LYMPHADENECTOMY AND ENDOMETRIAL CANCER

Type of Lymphadenectomy	No. of Cases	Positive Lymph Nodes	
		Number	Per cent
Radical	16	6	37.5
Selective	61	10	16.4
Fat only	3	0	0.0
Total	80	16	20%

TABLE VIII

SITES OF METASTASES OF ENDOMETRIAL CANCER*
(CLINICAL, SURGICAL AND AUTOPSY DATA)

Organ	Metastases (381 Cases)		Group I Before Definitive Therapy (42 Cases)		Group II Postoperative (Panhysterectomy) (339 Cases)	
	No.	Per Cent	No.	Incidence	No.	Incidence
Vagina	40	10.5	17	40.5	23	5.8
Cervix	32		8		24	
Urethra	5		2		3	
Vulva	2				2	
Clitoris	1				1	
Ovaries	49	12.8	7	16.6	42	12.4
Tubes	23		2		21	
Parametria	39	10.2	5	11.9	34	10.0
Bladder	19	5.0	4		15	
Rectum-sigmoid	23	6.0	3		20	
Peritoneum	19		4		15	
Omentum	14		3		11	
Liver	11		3		8	
Spleen	7		2		5	
Diaphragm	2				2	
Lung	21	5.5	9		12	
Adrenal	3				3	
Thyroid pituitary	2		1		1	
Kidney	2		1		1	
Bony skeleton	11	2.9			11	

* For lymph nodes see Table VII.

Table VIII, according to whether surgery had been employed or not. Most of these not operated upon received radium or roentgen therapy or both, and a few were terminal cases when first seen. Forty in all had evidence of vaginal metastases as part of a generalized carcinomatosis as shown in Table VIII. Comparison of Tables X and XI shows that 9 per cent of the acanthomatous cancers produced 20 per cent of the vaginal metastases.

Vaginal metastases must be interpreted as of serious omen and evidence of widespread carcinomatosis. Of the 40 cases,

TABLE IX

VAGINAL METASTASES IN RELATION TO TYPE OF TREATMENT

Treatment	Total No.	Vaginal Metastases	
		No.	Per cent
Radium alone or plus roentgen therapy	23	7	30.4
Radium plus hysterectomy	37	4	10.8
None prior to metastases	(381)	8	2.1
Postoperative, no radium	321	21	6.5
Total	381	40	10.4

TABLE X

EWING'S HISTOLOGIC CLASSIFICATION FOR ENDOMETRIAL CANCER

		No.	Per cent
Group I	Adenoma malignum	32	8.4
Group II	Papillary adenocarcinoma	315	82.7
Group III	Alveolar adenocarcinoma		
Group IV	Adenoacanthoma	34	8.9
Total		381	100.0

34 or 80.5 per cent were dead within five years or less after the initial diagnosis of endometrial cancer had been made. Only 2 cases have survived more than five years, and both of them had done so before the appearance of the vaginal metastases, five and eleven years respectively.

The authors' surgical-pathologic classification was designed to provide a basis for the evaluation of the five year follow-up of patients in whom the exact status of the endometrial cancer had been established. The results have been previously referred to.[9] These end results have been determined as shown in Table XII.

These follow-up results are compared with those reported by Heyman for primary radium therapy alone as shown in Table XIII.

SUMMARY

The authors' arguments against the routine use of preoperative radium may be summarized as follows:

1. Cancers located elsewhere are not usually irradiated prior to their surgical removal.
2. Ten per cent of our cases were Stage 0; and another 40 per cent had superficial myometrial invasion, making 50 per cent that had minimal disease.
3. Radium affects only the superficial lesions which will be removed anyway.
4. Current methods of intracavitary radium and external abdominal roentgen therapy are inadequate for deep myometrial invasion and spread beyond the uterus.
5. Surgery is prompt; the patient need not worry for an additional period of 6 to 8 weeks after the application of radium.
6. Prognosis should be determined in terms of the surgical pathology including positive and negative lymph nodes and not in terms of the therapy employed, i.e., preoperative radium versus no radium.
7. When lymph nodes are positive, vascular metastases are frequent.
8. Endometrial adenocarcinoma spreads via the blood stream like cancers of the prostate, bladder, kidney and rectum.

TABLE XI

VAGINAL METASTASES GROUPED ACCORDING TO THE HISTOLOGIC TYPES OF EWING

Histologic Type	Total No.	Vaginal Metastases		Percentage After Way
		No.	Per cent	
Adenocarcinoma	315	33	10.4	9.2
Adenoacanthoma	34	7	20.5	53.3

TABLE XII

FIVE YEAR FOLLOW-UP UNCORRECTED, BASED ON AUTHORS' SURGICAL-PATHOLOGIC CLASSIFICATION OF ENDOMETRIAL CANCER

	Total No. Followed	Five Year Survival	
		No.	Per Cent
Stage O	10	9*	90.0
Stage I	119	94	78.9
Stage II	34	17	50.0
Stage III	9	1	11.1
Stage IV	13	0	0.0
Total	185	121	65.4

* Died second day postoperatively of heart disease. This represents an uncorrected mortality rate, i.e., if the patient died of her medical disease, such as hypertensive cardiovascular-renal syndrome, she was included as having died of the cancer.

TABLE XIII

COMPARISON OF FIVE YEAR SURVIVAL RATES IN AUTHORS' SERIES WITH THOSE REPORTED BY HEYMAN USING HIS CLASSIFICATION

	Percentage	
	Heyman	Authors'
Stage I (limited to corpus excluding Stage O)	66.8	78.9
Stage II (extension beyond the uterus)	21.2	32.1
Total	61.8	65.4

9. Hematogenous spread, suspected in about 25 per cent of the cases, needs to be treated by the intravenous route, in a manner yet to be discovered.
10. The way to stop a run-a-way horse is to get out ahead of it, and not by running after it, as we are doing now with radium alone or combined with surgery.
11. The present uncorrected cure rate of endometrial cancer with surgery alone or followed by postoperative irradiation is already in the neighborhood of 65 per cent.
12. Radium interferes with the histologic study and grading of the type of cancer.
13. Two hospital admissions, and two operations are more expensive than one.
14. Some irradiated patients refused to return for the operation.
15. Perforation of some uteri with advanced disease militates against the insertion of radium.
16. Vaginal recurrences are not due to spread of the cancer by the operation but represent spread of the disease, especially when the cancer is of the adenoacanthoma variety.
17. Vaginal recurrences are not reduced by preoperative insertion of radium.

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CANCER OF THE FLOOR OF THE MOUTH

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THIS paper is based on a study of 40 cases of malignant tumors of the floor of the mouth treated at the Radium Institute of Santiago, Chile between May, 1930 and May, 1949.

Definition. The floor of the mouth is the anatomic region limited between the lower gum anteriorly, the frenulum of the tongue posteriorly in the midline and the base of the anterior tonsillar pillar posteriorly on the lateral sides. It has a crescent shape. Malignant tumors in this region have no particular features, but due to the anatomic configuration of the floor itself, any treatment either surgical or radiotherapeutic is difficult to apply. In reference to metastases we need to add that lymphatic drainage of the floor of the mouth is taken not only by the submaxillary filter, but also by the midcarotid or even supraclavicular lymph nodes.

Incidence. In this report an analysis of 40 cases of malignant tumors of the floor of the mouth admitted to the Radium Institute in a nineteen year period (1930–1949) is presented. During the same years we have seen 13,300 patients with cancer of different locations, and among them there were 518 cases of cancer of the mouth. This means that cancer of the mouth comprises 3.89 per cent of all our cancer patients, and cancer of the floor of the mouth about 7.7 per cent of all malignant tumors located inside the mouth (Table I). Therefore, this is not a frequent type of cancer and according to our figures we have only seen about 2 new cases per year. It is our feeling that these figures represent almost all of the cases seen in this country as our Institute, being the only service with adequate facilities for treating this type of lesion, receives all patients with cancer of the floor of the mouth.

TABLE I

ANATOMIC DISTRIBUTION OF 518 CASES OF MOUTH CANCER

Lip	259 cases
Tongue	151 cases
Cheek	57 cases
Floor of mouth	40 cases
Gum	11 cases

Age. In our series the youngest patient was twenty-seven years of age (undifferentiated sarcoma) and the oldest eighty-two. The larger group of cases was found between the ages of fifty-one and sixty (Table II). Seventy-seven of all the patients were over fifty years of age. This is probably explained by the fact that many epithelial tumors are very slow growing and take years of intraepithelial development before they show signs of clinical manifestation.

Sex. Of our 40 cases, 38 were men (95 per cent) which shows that this type of cancer occurs almost exclusively in the male. There is no adequate answer for the sex predominance of cancer of the floor of the mouth, but it is possible that an explanation will be found when we know more about disturbances originating in epitheliums in connection with hormonal pathology.

Delay in diagnosis. The average time before consulting the Cancer Institute was about 6.5 months. The patient who came earliest had symptoms for about a

TABLE II

Age	No. of Patients
20–29	1
30–39	1
40–49	6
50–59	18
60–69	9
70–79	4
80–89	1
Total	40

month, and the one who delayed the longest had four years of history; both cases are alive and well. Does this mean that early diagnosis is not important for considering prognosis? Our group is too small to draw any conclusion, but it has been stated before in cancers of other locations that the final prognosis is somewhat independent of the time of evolution.

Predisposing factors. For many years it has been stated that chronic irritation, syphilis, tobacco and ill-fitting dentures are predisposing factors in the development of mouth cancer. In reference to this location we feel that external chronic irritation is of very minor importance. The floor of the mouth is almost completely protected from trauma produced by ill-fitted dentures. Moreover, we have seen cancer develop in an edentulous patient and as far as syphilis is concerned only 15 per cent of our cases had positive serologic reactions. Of all these predisposing factors, it seems that leukoplakia is the only one important as a precancerous condition. We have observed several leukoplakias which have developed into cancer and we have also seen a number of cases in which a clinical leukoplakia after removal showed carcinoma *in situ* on pathologic examination.

Symptoms. Cancer of the floor of the mouth has no particular symptomatology. Any ulcerated lesion which does not heal in two to three weeks should be submitted to biopsy and histopathologic examination. It has been noted that in some of our cases the early lesion corresponded to a non-ulcerated tumor which later destroyed the mucous membrane and became ulcerated. In other cases, pain related to the tongue and propagated to the ear presented as the initial symptom. This pain in the tongue is explained by the fact that the lingual nerve runs very superficially beneath the mucosa. As the lingual nerve has an anastomosis with the chorda tympani, the pain can also radiate to the ear. In few instances the first sign observed was an indurated mass in the submaxillary region with the typical features of a lymph node metastasis. The primary lesion was usually ulcerated and had a tendency to invade the adjacent organs such as the tongue in 55 per cent of our cases, the gum in 25 per cent and the mandible in 17 per cent.

TABLE III

LYMPH NODE METASTASIS

Total number of cases	40
With metastasis on admission	5
With metastasis later on	6
Total number with metastasis	11 (27.5 per cent)

Lymph node metastasis. In the entire group of 40 cases, a clinical diagnosis of lymph node metastasis was made in 18 on admission; of these, 13 were operated upon and the histopathologic examination showed metastasis only in 5. Of the 22 remaining cases which did not have metastasis on admission, 6 developed secondary deposits in lymph nodes subsequently. This means that metastases were present in 11 cases or in 27.5 per cent of all patients (Table III). According to our figures it is evident that the submaxillary and submental lymph nodes are the most frequently invaded.

Pathology. Epidermoid carcinoma Grade 1 was present in 92 per cent of all cases; there were 2 undifferentiated carcinomas and one sarcoma (Table IV).

Treatment. Any treatment applied requires a close collaboration between the surgeon, radiotherapist, and the dentist.

Hygienic preparation of the mouth. No matter what the treatment of choice, general hygienic measures should always be applied first. These include careful exami-

TABLE IV

Pathologic Reports	No. of Cases
Epidermoid Grade 1	35
Epidermoid Grade 4	2
Sarcoma	1
Malignant mixed tumor	1
Not stated	1
Total	40

TABLE V

TUMOR DOSE IN SUCCESSIVE CASES

Type of Treatment	Dose	Duration Days	Necrosis
Radium implant	8,000 gamma r	14	—
Radium implant	7,000 gamma r	8	—
Implant plus radium to skin of neck	14,000 gamma r	13	+
Implant plus radium to skin of neck	13,000 gamma r	13	+
Radium implant	11,000 gamma r	7	+
Radium implant	9,000 gamma r	7	+

nation by a dentist, extraction of all carious teeth and removal of the metallic prostheses in the lower gum close to the floor of the mouth. Radiation treatment after extraction should not start until the tooth socket is healed. This is very important in order to prevent future radionecrosis of the mandible.

Treatment of the primary lesion. Most of our cases have been treated by implantation of radium needles containing 1.3 or 2.6 mg. of radium filtered by 0.5 mm. of platinum. The active length of the needles was 2 and 4 cm. respectively. Theoretically, this is a good treatment, but from the practical point of view it is very difficult to obtain a uniform dosage distribution for a volume implant because of the particular shape of the floor of the mouth. The maximum tumor dose may produce undesirable "hot spots" with danger of necrosis, while a minimum dose may not be enough to destroy the tumor. A more uniform distribution can be obtained sometimes by adding external irradiation to the implant with a moulded apparatus loaded with radium at 5 or 6 cm. distance. Among our cases successful results were obtained only in patients treated either by a volume implant or by an implant plus radium applied externally to the submental region (Table v). It is interesting to note that among the successfully treated cases, 4 of 6 developed necrosis after treatment and this happened every time the tumor dose exceeded 8,000 gamma r.

Radium applied intraorally in a surface applicator seems inadequate because it is difficult to maintain in place and also because the surface dose diminishes rapidly towards the depth of the lesion. Roentgen therapy applied externally is a good treatment theoretically. However in our group we had no successful results with this method. It must be remembered that all cases treated with roentgen rays were far advanced from the start. We have had no experience with roentgen therapy applied intraorally.

As far as surgery is concerned it is our feeling that intraoral procedures have no place in the treatment of cancer of the floor of the mouth. The only justified procedure is the "en bloc" resection of the tumor plus the adjacent portion of the tongue and removal of half of the mandible. If metastatic lymph nodes are present a radical neck dissection ought to be done at the same time. Hemimandibulectomy is necessary in order to obtain a perfect closure and to avoid local recurrence. It has been shown that in 50 per cent of these cases lymphatic pathways run through the periosteum of the mandible and this is another reason for removal of the mandible.

Treatment of lymph node metastases. In our patients, lymph node metastases were found in 27.5 per cent of all cases. In spite of this low figure our present policy is to operate on the submaxillary and submental region prophylactically after having treated the primary lesion with radium. We do this mainly because patients do not return at regular intervals for follow-up, and in many instances they come back with large, inoperable lymph nodes of the neck.

If metastatic lymph nodes are present at the first examination and proved by aspiration biopsy, a radical neck dissection is the procedure of choice. We have started recently with resection of the floor of the mouth plus hemimandibulectomy, and therefore we have no experience in end-results with this type of surgical approach.

Results. Of the 40 cases analyzed in this series, 2 were too far advanced for any kind of treatment. Among the remaining 38, 6 have a survival of five years (15.7 per cent). Studying the successful cases we find that none of them had lymph node metastasis or invasion of the gum. Four of these had limited invasion of the adjacent tongue. It seems therefore that invasion of the gum or metastatic lymph nodes are important factors in final prognosis. If we study the results of treatment in relation to delay in diagnosis, it can be seen that the average time of evolution before treatment was 10 months in the successful cases as against 5.4 months for the failures. There is no logical explanation for the good results obtained in the cases with a longer period of evolution. At any rate we still feel that early diagnosis is important because such cases have less chance of developing lymph node metastasis or invasion of the adjacent structures.

SUMMARY

Cancer of the floor of the mouth is not common. It represents 7.7 per cent of all mouth cancers in our group. Curability of this type of cancer is strictly dependent on the local extension of the tumor when first seen. Our best results were obtained by volume implantation of radium needles followed by external application of radium. Optimal tumor dose appears to be 7,000 gamma r in seven to eight days. Cases receiving 14,000 gamma r in less than fourteen days are apt to develop necrosis.

If there is invasion of the gum or evidence of lymph node metastases on admission, we advise the surgical approach: resection of the floor of the mouth plus hemimandibulectomy and a radical neck dissection. If lymph node metastases are not present on admission, we treat the primary lesion with a radium implant. This is followed by a prophylactic submaxillary and submental dissection.

The five-year cure rate of 38 cases followed after treatment is 15.7 per cent.

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THERAPY OF CARCINOMA OF THE URINARY BLADDER*

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FOR decades carcinoma of the urinary bladder has had the dubious distinction of being one of the most controversial subjects in the study of cancer. The urologists and cytologists differ over the diagnosis and the surgeons argue over the procedures of operation.

To add to the confusion, the advent of radiation therapy has thrown another obstacle into the course toward a definite plan of procedure in treating these cases. Moreover, the radiologists have not agreed upon any systematic plan of therapy. A review of the literature concerning the various types of treatment fails to reveal any adequate method.

This discussion is based on the study of 103 consecutive cases of carcinoma of the urinary bladder treated by our radiological department in cooperation with the department of urology. The authors are satisfied that radiation therapy is the method of choice, at least at the present time, and this can be either alone or in conjunction with *simple* surgical procedures. The figures will show that better results are obtained when the surgeon and the radiologist work as a team in combating the disease, rather than as parties of opposition.

It is our aim to establish this premise as a fact and to present what we have found to be an expedient and successful plan of procedure in the therapy of carcinoma of the urinary bladder.

First of all, we must know the nature of the lesion we are going to treat. Most authors agree upon the comparatively simple classification which divides bladder carcinoma into two main headings: 1. papillary type; 2. non-papillary or infiltrating type. Each of these are further defined according to cellular type and are graded according to activity.

The papillary type will include those formerly benign papillomas which have undergone malignant changes and are the cause of so many errors of judgment on the part of the cystoscopist who may decide the fate of the patient by the gross appearance of the lesion. The non-papillary type may be either ulcerative or nodular in character.

In either type one cannot estimate the degree of malignancy, the extent of infiltration, or the presence of metastases on the gross appearance of the lesion alone; and furthermore, as Cade points out, it is more disheartening to know that the microscopic findings can be misleading as well. This is due to the fact that small biopsies can completely miss malignant portions of a papillomatous tumor and show only the innocent appearance of benign villous epithelium, for such tumors are characteristically a mixture of widely dispersed clumps of malignant cells in a large field of benign tissue. Thus, to establish a diagnosis requires the exercising of the maximum of good judgment and scientific investigation. Once a diagnosis has been established, there remains a choice of treatment. At the present time this choice is limited to: 1. surgical excision or fulguration; 2. radiation therapy; 3. the questionable adjunctive treatment with hormones.

The surgical procedures include transurethral resections, suprapubic resections, partial cystectomy, and total cystectomy with transplantation of the ureters. The published results of the various procedures belie the conclusion that one method has anything but technical advantages or dis-

* Presented at the Thirty-seventh Annual Meeting of the American Radium Society, Washington, D. C., April 21–23, 1955.

advantages over the others. It is apparent that their successes are directly proportionate to the nature and the extent of the lesion and not to the type of procedure. Concerning the more radical procedures, we would agree with Cade when he states that "The magnitude of the operation, the high operative mortality, the chances of local recurrence, and the grave disability following total cystectomy remain formidable obstacles." To compare the results of surgical procedures with those of radiation therapy in any form is not logical unless the studies are made on patients with somewhat comparable lesions. The surgical procedures are certainly far from being superior when only comparable lesions are considered.

Radiation treatment includes: 1. roentgen therapy, either of the closed, external type, or the contact type through a suprapubic wound into a marsupialized bladder; 2. radium therapy, either with needles implanted into the tumor or with a plaque or a bomb placed within the bladder; 3. the implantation of radon seeds into the tumor or its site. Of these choices, it can be said that all of them have been tried separately and in combination. The literature is abundant with reports of sporadic cases and series of cases treated with successes and failures, all intent upon establishing one particular method as the one and only treatment to use. In too many instances, conclusions are based upon illogical data with no plan of approach for the radiotherapist to follow in the treatment of cancer of the urinary bladder.

In planning the course of action, the correct diagnosis is of primary importance. Then one must consider the extension of the disease. It has already been pointed out that there is great difficulty in estimating the extent of any lesion. We feel that whenever the diagnosis of carcinoma of the urinary bladder is made, the patient should receive the benefits of radiation therapy, whether or not there is any evidence of local extension.

Another important consideration should be the general condition of the patient. Most frequently this is underestimated. The usual conception is that if the general condition of the patient contraindicates surgery, radiation therapy is indicated. But with the exception of specific contraindications as, for example, cardiovascular disease, the biological effect of ionizing radiation makes it impossible for such patients to support a treatment of the magnitude of an adequate radiation therapy.

Because of the marked reaction of the bladder to radical radiation therapy, two factors pertaining to the patient's general condition must be attended *before* therapy is instituted. First, there must be satisfactory drainage of the urinary bladder. If there is an obstructing prostate gland or the tumor mass itself blocks the urinary flow, the surgeon is obligated to resect and establish adequate drainage. Second, any bladder infection which might be present should be combated vigorously. One factor afforded by radiation therapy which is closely related to the general condition of the patient is excellent psychological effect of being treated as an out-patient without having to endure a long hospital stay and formidable surgical procedures. Lastly, one has to consider previous therapy. Here the utmost understanding between the surgeon and radiotherapist is necessary. If it is determined that surgery is indicated, the surgeon should consider the procedure from the standpoint of the radiation therapy to follow, remembering that maximum tolerated doses must be given if the patient is to be benefited. Fresh surgical incisions certainly hamper attainment of this goal.

Within the realm of radiation therapy, one is sometimes called upon to treat with one type of radiation a case unsuccessfully treated with some other type. We can agree in this respect that cancer therapy by irradiation is an all or none procedure. If the first attempt fails, further irradiation may lead to grave complications. This does not mean, however, that recurrences can not treated. It does mean that extreme caution and vigilance must be exercised

during the repeated courses so as not to cause irreversible tissue damage. This is certainly a strong point leading to our conclusion that in radiation therapy of carcinoma of the bladder, the therapist should be sure of a sufficiently large dose the first time.

We believe that the ideal relationship between the surgeon and the radiologist has been attained in the handling of our series of cases and we further feel that this has been of major importance in the successes achieved. We were fortunate in that all of the cases in our series were handled in cooperation with one urological group, (namely—R. Lee Hoffman, M.D.). The basis of this cooperation is briefly this. The complete *cure* of the patient's disease is the goal in every case. Therefore, the urologist depends upon the radiotherapist to give a cancerocidal dose to any remaining tumor tissue that may be present. For this reason we feel that his procedures are an adjunct to ours and he looks upon radiation therapy as an adjunct to his.

We have come to our conclusions partly by interpretation of the reports of the past and partly by the results of following what we believe to be a systematic procedure for treating cancer of the urinary bladder. Our series of cases is not similar to many others reported in the literature in that it includes all types of primary carcinoma of the bladder in various stages of malignancy. No differentiation is made as to age, sex or general condition of the patient. The ages range from twenty-six to eighty-seven years with an average of sixty years. Of these, 73 per cent were males.

Table I

TUMOR TYPES

Grade	I	II	III	IV	Total
Papillary squamous cell	28	27	15	3	73
Papillary transitional cell	3	10	3		16
Adenocarcinoma					3
Not classified or graded					11
					103

Table II

TYPES OF RADIATION THERAPY

Radium alone	1
Radon alone	3
Roentgen therapy alone	75
Roentgen therapy and radium	7
Roentgen therapy and radon	15
Roentgen therapy, radon, and radium	2

From these figures it would seem that the papillary type of bladder carcinoma is by far the most common. Moreover, the figures are so one-sided that it would not be fair to draw any conclusions as to the radio-vulnerability of the various types. It is generally stated that the papillary tumors which have not invaded the wall of the bladder are the most suitable for radiation therapy. However, Colby and Sniffen at Massachusetts General Hospital reported 130 cases treated and they concluded that the papillary and non-papillary types responded about equally and believe there is no relation between histology and expected response to radiation therapy.

The type of therapy varied somewhat according to the individual case, which is as it should be. Surgically, all the cases were biopsied, 95 by transurethral approach and 8 by suprapubic cystotomy. In no case was radical surgical resection done. Radiation therapy consisted of the use of radium, radon seeds, and roentgen rays, either singularly or in combination.

A single course of radiation therapy was given to 81 patients; 15 required two courses; and 7 were given three courses. One patient who had received three courses of therapy later developed a new lesion on the opposite side of the bladder and a fourth course was given. The roentgen dose averaged 11,500 r as measured in air per patient. In many instances, the depth or tumor dose was better than 6,000 r which is the level for which we strive. This dose was delivered with 200 kv. roentgen rays, composite Thoraeus filter, 50 cm. target skin distance, 2.8 mm. copper half-value layer, through six pelvic ports and in frac-

TABLE III

SURVIVAL RATES

Total cases	103
Inadequate follow-up	13
Dead from other causes	6
Remaining cases	84
Living without malignancy	36 (43%)
Living with residual or recurrent malignancy	7
Dead from malignancy	41

tions of 300–400 r daily.

Radon seeds were reserved for implantation of smaller tumor beds following fulguration of the tumor. We ordinarily use 1 mc. seeds with the usual 1 cm. distribution throughout the area involved, the implantation being done through the cystoscope.

Radium implantation was used in larger areas or in nonresectable tumors through a suprapubic incision. The implant, with low intensity needles, was calculated to give a dose of 4,000 to 5,000 gamma r minimum to the affected area. The use of either radon or radium does not preclude the use of external irradiation and in all cases a roentgen dose of 6,000 r should be the goal.

Significant statistical results are compiled from these cases. Twenty-four (29 per cent) of these cases have survived for five or more years.

Comparing these results with published results of other therapists, we feel that this program for treating patients with carcinoma of the urinary bladder is the most logical, safe, and thus far the most successful. The complications of fibrosis, strictures, and fistulae—so often used as an argument against radiation therapy—are not an inherent result of the method. They are rather the fault of the therapist who treats his cases too rapidly and without due vigilance as to the patient's response. We admit that they do occur; they are unfortunate, but they certainly are not inevitable as some opponents would have us believe. For instance, we have never produced, as far as can be determined, any irrevocable damage to normal ureters.

TABLE IV

SURVIVAL INTERVALS

Years	No. of Patients
2	6
3	9
4	6
5	3
6	3
7	9
8	2
9	1
12	1
15	1

CONCLUSION

The following is a summary of the program thus presented as the most logical and functional plan for the radiologist to follow in the therapy of carcinoma of the bladder:

1. With the surgeon and pathologist, make a definite diagnosis.
2. With the surgeon, decide on the type of therapy to be employed considering especially: (a) the extension of the malignancy; (b) the patient's general condition; (c) previous treatment.
3. Influence the surgeon, if possible, to limit his surgery to biopsy unless more extensive surgery is needed to establish adequate urinary drainage.
4. Treat urinary tract infections vigorously.
5. In certain feasible cases take advantage of the application of radon and radium where its use can be made without radical surgical procedures.
6. In *all* cases of carcinoma of the urinary bladder, give deep roentgen therapy and give it to the maximum of the patient's tolerance.
7. Be discerning and watchful of the patient's reaction and response to therapy in order to avoid complications. If untoward reaction occurs reduce the fractionated dose rather

than prolong the interval of treatment.

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DISCUSSION OF THE PAPER BY DRS. LOCKWOOD AND CHAPMAN

T. A. WATSON, Saskatoon, Canada. This paper demonstrates the necessity for the use of different types of radiation therapy, usually in conjunction with surgery, in various types of cancer of the bladder. An excellent illustration is thus provided of the obligation, in any department of radiotherapy, of having available a wide variety of equipment so that the needs of each individual patient and tumor can best be served. We have heard described, for example, the use of intracavitary superficial "contact" therapy, external roentgen therapy, radon seed implantation, radium implantation, and irradiation by a central source in the bladder. One might also add that papillomatosis is being successfully treated in some centers by the introduction into the bladder of a bag containing radioactive isotopes. This should make us realize that no radiation therapy department can be considered as satisfactory, and of being capable of offering every patient the best chance of benefit, unless various types of roentgen therapy apparatus, radium and radon, and isotopes are available.

Dr. Lockwood has pointed out that patients should not be refused treatment on the grounds of advanced age or poor general condition. We are dealing with a disease which is fatal if left unchecked, and the only contraindication to treatment should be such poor general condition that the patient would be unable to survive the indicated course of treatment. This means, of course, that in the advanced cases statistical results will be poorer, but this constitutes no justification for withholding treatment. I note that Dr. Lockwood advocates the insertion of radon seeds, in certain types of tumor through the cystoscope. I am of the opinion that any radon seed implantation is better and more accurately performed through a cystotomy wound. I was interested in hearing that following transurethral fulguration Dr. Lockwood treats even a case of early malignant papilloma with external radiation. In most centers the fulguration for this type of tumor is considered sufficient and I wonder whether Dr. Lockwood has any control series of similar cases which have been treated by fulguration alone to compare with his results in this group. Dr. Lockwood feels that every patient should have a course of external irradiation, preferably to a tumor dose of 6,000 r even after radium or radon seed implantation. The dose of 6,000 r seems very high, especially when 200 kv. is used.

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SUPERVOLTAGE ROENTGEN THERAPY IN CANCER OF THE LUNG*

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CANCER of the lung is very much in the news these days but very little is being done for this disease from a curative point of view. If all cases are considered, five year survivals from surgery are insignificant in number because the great majority of cases are inoperable and, of the minority which undergo resection, only a small percentage is cured. No one claims that radiation therapy is curative in this disease although isolated five year survivals have been reported. Most of us, however, know of the occasional person who has survived five years without any treatment at all, and, presumably, if this type of patient were seen early in his disease, then treatment of any kind would produce a five year survival.

At the present time in most centers the best and earliest cases are abandoned to the surgeon; thus, the radiotherapist must do what he can with the less favorable remainder. If any significant palliation can be obtained in this group, then a useful purpose will have been achieved.

In the Saskatchewan Cancer Clinics from 1932 to 1953, 611 cases of cancer of the lung have been diagnosed. Table 1 sets out these patients in their various groups with respect to treatment and survival. The survival, naturally enough, is poorest in the untreated group which, also, represents the most advanced cases. One hundred fifty-one cases were treated with roentgen therapy alone but most of these cases fall into the period 1932 to 1944 and the average survival is only a little better than that of the untreated cases. One must also take into account the fact that the patients treated by roentgen rays alone were unlikely to be so advanced on the average as the untreated cases. From these figures, therefore, roentgen treatment alone would seem to offer very little. The average survival of patients treated with the cobalt unit or betatron is considerably better and these cases will be described in greater detail a little later. An interesting point to notice here is that those patients treated with roentgen rays and nitrogen mustard showed quite a long survival period whereas the figures for those treated with roentgen rays alone or nitrogen mustard alone were quite poor. Figure 1 depicts graphically the survival of patients after various types of treatment. These curves are corrected so that the percentage of survivals shown at any particular time is a percentage of the number of cases exposed to risk at that time. It will be seen that the untreated cases die rapidly, there being only 2 cases alive out of a total of 319 at the end of three years. The curve for the patients treated with roentgen rays alone follows fairly closely that of the untreated cases excepting that more survive in the early months. This is probably due to the fact that some of the untreated patients were terminal when first seen and died rapidly. The betatron-treated patients show the greatest survival in the early months and thereafter fall fairly rapidly. The total curve, however, is not too different from that exhibited by the patients treated by pneumonectomy and it is in this latter group in which all the most favorable cases are found. In this group there is only one five year survival following pneumonectomy. It was considered that there were too few cases treated with cobalt for inclusion in this graph but the curve of the cobalt-treated patients is somewhat less favorable than that of the patients treated with the betatron.

* Presented at the Thirty-sixth Annual Meeting, American Radium Society, Hot Springs, Virginia, March 14–16, 1954.

TABLE I

SASKATOON AND REGINA CLINICS

Survival of Carcinoma of the Lung (611 cases) 1932–1953

Type of Treatment	No. of Cases	No. Alive	Average Survival of Living	No. Follow-up	No. dead	Average Survival of Dead
Untreated	319	14	15 mo.*	10	295	3.1 mo.
Roentgen-ray	151	5	12 mo.	1	145	5.7 mo.
Betatron	28	5	20 mo.		22	8.0 mo.
Cobalt-60	14	7	7.6 mo.		7	5.9 mo.
Radical surgery	54	17	26 mo.		37	7.0 mo.
Pall. surgery	10	1	2 mo.		9	5.4 mo.
Thoracotomy alone	29	1	1 mo.	1	27	2.8 mo.
Thoracotomy and other radiation treatment	25	3	10.6 mo.	1	21	8.0 mo.
Thoracotomy and/or other treatment	54	4	8.2 mo.	2	48	4.5 mo.
Roentgen-ray and nitrogen mustard	21	1	14 mo.		20	9.9 mo.
Nitrogen mustard alone	14	0		1	13	4.6 mo.

* Includes two living untreated cases, four years and three years, four months (both pathologically proved).

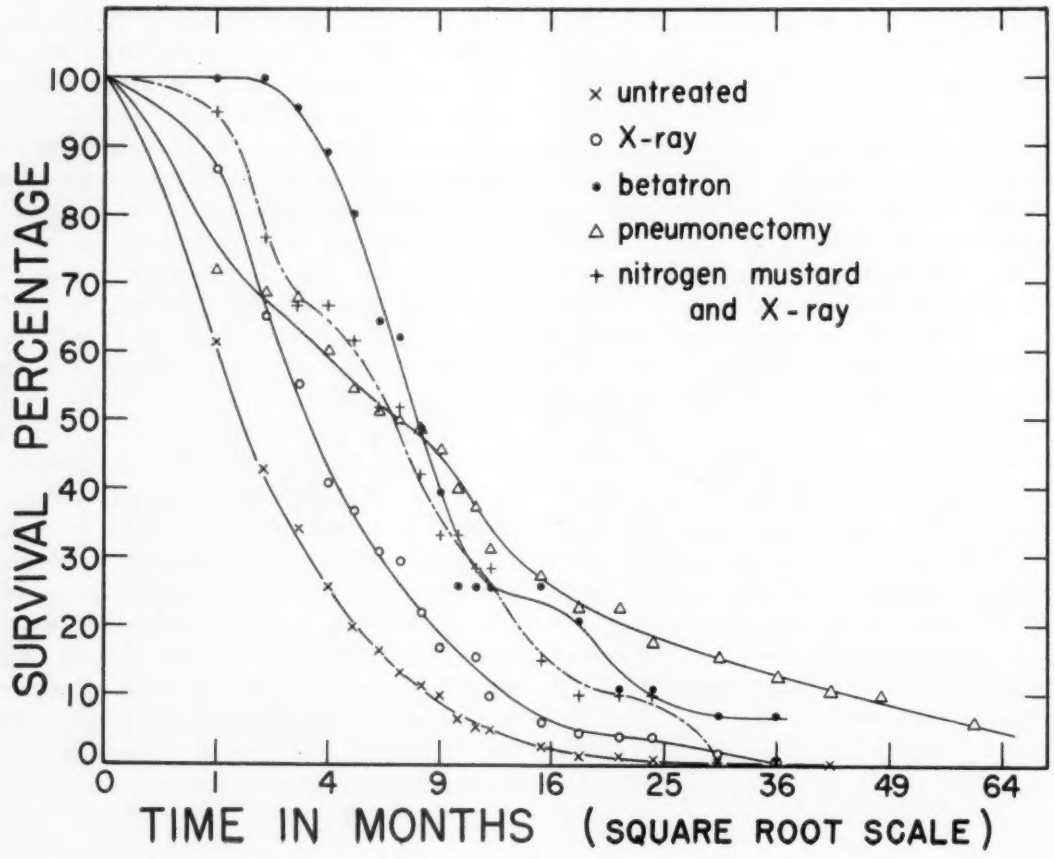

FIG. 1

Table II

Type of Tumor (465 proved out of 610 cases of lung carcinoma—61 per cent)

Type	No.	Per cent
Epidermoid	83	18
Anaplastic	73	16
Adenocarcinoma	46	10
Alveolar cell	5	1
Mixed or unstated type	258	55
Total	465	100

Table II shows the distribution of types of lung cancer in all cases. It is seen that the most favorable results are obtained with pneumonectomy from epidermoid types of growths. This is in accordance with other published literature. A similar distribution is seen in Table III in the cases which were treated with the betatron. Only 5 cases out of 27 are alive but the survival times of both the alive and dead patients are greater in the epidermoid type of cancer.

Since we are concerned with palliation only, in the radiation treatment of cancer of the lung, an attempt has been made in Table VI to determine which types of treatment give the most palliation. The first two vertical columns show "subjective" and "objective" improvement noticed in the patient. "Subjective" improvement is a rather nebulous conception and consists merely in the recording of information in the chart showing that the patient either feels better, has gained weight or has less symptoms than previously. No distinction in time is made. "Objective" improvement means that there is roentgenologic evidence of regression of the tumor. The third vertical column "both" means that the patient both felt better and that there was

Table III

CARCINOMA OF THE LUNG

Type of Tumor
Betatron (27 cases)

	Adenocarcinoma		Epidermoid		Anaplastic		Unstated or Mixed	
	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead
		4 mo. 12½ mo.	31 mo. 19 mo. 5 mo.	2 mo. 13 mo. 7 mo. 10 mo. 20 mo.		5 mo. 10 mo.	40 mo. 6 mo.	6 mo. 5 mo. 6 mo. 2 mo. 7 mo. 8 mo. 9 mo. 10 mo. 2 mo. 9 mo. 15 mo. 4 mo. 8 mo.
Total Cases	—	2	3	5	—	2	2	13

TABLE IV

CARCINOMA OF THE LUNG

Type of Tumor
Cobalt 60 (14 cases)

	Adenocarcinoma		Epidermoid		Anaplastic		Unstated or Mixed Type	
	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead
			9 mo.	2 mo. 16 mo. 3 mo. 9 mo.		4 mo. 2 mo.	3 mo. 8 mo. 16 mo. 11 mo. 5 mo. 1 mo.	5 mo.
Total Cases	—	—	1	4	—	2	6	1

also roentgenologic evidence of improvement in the lung tumor. The final column (percentage improvement) includes the first three columns (subjective, or objective improvement or both) and is expressed as a percentage of the total. It will be seen that only a very small number of cases improved which were treated with roentgen rays alone or nitrogen mustard alone. With the betatron, cobalt 60, or nitrogen mustard and roentgen therapy, however, the percentage improvement was quite significant.

Twenty-seven patients have been treated using the 23 mev. betatron. All of these patients were section proved and were considered inoperable either from the point of view of age and general condition or from purely surgical considerations. All of these cases were treated with large fields which included the primary tumor and more than half the mediastinum on the same side as the lesion. This was done in an attempt to include the lymphatic drainage areas. The tumor dose, given in these cases was either 5,500 roentgens to 6,000 roentgens in a period of eighteen to twenty days (fifteen treatment days) or 7,500 roentgens over a period of thirty to thirty-five days (twenty-five treatment days). Almost all cases, also, developed a dysphagia towards the end of treatment, due to the inclusion of the esophagus in the treated volume. There was no true radiation sickness in this group. Of the 22 patients who are dead, postmortem examination was performed only in 5 and in each of these cases traces of the primary tumor were found in the lung and there were usually distant metastases as well. There are 5 patients still alive, the longest period being forty months. This patient has bone metastases but no symptoms referable to his lung.

Fourteen cases have been treated using the cobalt unit. Eleven of these patients were treated with large fields, the tumor

TABLE V

CARCINOMA OF THE LUNG

Type of Tumor
Betatron and Cobalt 60

Adenocarcinoma		Epidermoid		Anaplastic		Unstated or Mixed	
Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead
0	2	4	9	0	4	8	14

TABLE VI

CARCINOMA OF THE LUNG

SASKATOON AND REGINA CLINICS

Improvement after Treatment

Type of Treatment	Subjective	Objective	Both	None or ?	Total	Per Cent Improvement
Roentgen-ray	30	2	32	87	151	42.5
Betatron	7		13	7	27	75
Cobalt-60	4	1	6	3	14	79
Roentgen-ray and nitrogen mustard	7	1	7	6	21	72
Nitrogen mustard	2			12	14	14
	Improvement			None or ?		
Radical surgery	22			32	54	41
Palliative surgery	3			7	10	30

dose usually being 4,500 roentgens in an over-all period of seventeen to twenty days (fifteen daily treatments) and the maximum skin dose varying from 3,000 roentgens to 5,000 roentgens. The remaining 3 cases were treated with smaller fields to the primary tumor only using rotational therapy. All of these 3 patients who were treated with rotation are alive and well at the present time, although the longest survival is only nine months. The tumor dose given the rotational patients was 6,000 r in thirty to thirty-two days (twenty-five treatment days). There was no skin reaction in these patients and no constitutional effect.

In all patients treated either by the betatron or the cobalt 60 unit, excepting for 3 who were treated with rotation on the cobalt 60, large fields were used in an effort to include both the primary tumor and the lymphatic drainage area. Palliation obtained under these circumstances was much more marked with the betatron than with the cobalt unit. The 3 patients in whom the primary tumor only was treated, however, have shown remarkably good palliative results. We are now trying to decide whether it is preferable, from the point of view of palliation, to treat a very large volume or to confine one's attention to the primary tumor only. In the case of the betatron we intend treating all future cases of cancer of the lung with nitrogen mustard followed by large-field betatron radiation. The reason for so doing is that our figures for roentgen therapy combined with nitrogen mustard are very much better than nitrogen mustard alone or roentgen therapy alone. Since the results from betatron treatment are much better than roentgen therapy alone, then it would seem logical to combine nitrogen mustard and the betatron.

CONCLUSIONS

Supervoltage roentgen therapy seems to offer nothing curative in cancer of the lung. There is, however, evidence of significant palliation. It is suggested that nitrogen mustard combined with supervoltage radiation may be superior to radiation alone.

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THE EFFECT OF ACTH AND CORTISONE ON RADIATION PNEUMONITIS*

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RADIATION treatment of malignant disease is dependent first upon, the reaction of the tumor cell and its bed, and second upon the degree of injury produced in the surrounding normal structures. Clearly, the ideal situation would be one in which the tumor cells are eliminated with no damage to the normal tissues. In practice the physician using irradiation as a means of treatment is dealing with a delicate balance of damage to the tumor cell and to the normal cell. Only rarely can a cancer be cured without detectable damage to one or more of the surrounding normal structures.

The response of normal tissues varies appreciably to radiation. Normal lung tissue is one of the most sensitive. This sensitivity is clinically expressed as acute or chronic pneumonitis or fibrosis, and sharply limits the amount of radiation that on average can safely be given to the lung.

In theory, it is reasonable to assume that the response to irradiation of tissues, normal or abnormal, is modifiable. Abundant evidence from the laboratory has accumulated in the recent past that this is so. If it were possible to modify the response of the normal lung to radiation, then the hazard of current irradiation practices would be diminished.

This study reports such an attempt with ACTH and cortisone. Unhappily, the result is a negative one. As such, it is intrinsically of limited interest, but in view of other reports with differing conclusions in the literature it seemed worthwhile to record our experience.

Radiation pneumonitis is a complication of irradiation of the lung during and after treatment of intrathoracic and extrathoracic diseases. It can be serious with progressive respiratory distress and may result in death. Since the discovery that ACTH and cortisone have an inhibitory effect on the inflammatory process and on the formation of granulation tissue, they have been used therapeutically in a variety of lung conditions which have a tendency to form granulomas and fibrosis, such as sarcoidosis, silicosis and berylliosis. In some instances beneficial effects have been reported. Following this line of reasoning, ACTH and cortisone also have been used in preventing and treating radiation pneumonitis, with favorable results reported. However, the study of 15 cases treated at Memorial Center do not completely support this conclusion. The purpose of this paper is to record our experience with the use of ACTH and cortisone in radiation pneumonitis both as a preventive and as a therapeutic measure.

REVIEW OF LITERATURE

In 1951, Cosgriff and Kligerman[3] reported one case in which ACTH and cortisone were given for an acute radiation pneumonitis. There was marked improvement in the symptoms and partial clearing of the pneumonitis. The authors believed these changes were due to ACTH and cortisone. This case developed radiation changes of atelectasis and fibrosis two months after the cessation of ACTH and cortisone.

In 1953 Bluestein and Roemer[1] reported another case in which bilateral pneumonitis developed after radiation therapy to both sides of the chest wall for recurrent carcinoma of the breast. The use of cortisone, 100 mg. daily, and penicillin, 600,000 units per day, relieved the acute symptoms of dyspnea and cough. Three months later

* This work supported by grants in aid from the United States Public Health Service and from the Armour Research Corporation. Presented at the Thirty-seventh Annual Meeting, American Radium Society, Washington, D.C., April 21–23, 1955.

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Table I

AGE, SEX, LESION AND FACTORS OF RADIATION THERAPY

Case No.	Age	Sex	Primary lesion	Sites Irradiated	Field cm. Size	Kv.	Target skin distance (cm.)	Tissue Dose (r)	Time in Days
I	29	M	Fibrosarcoma, thigh	Right middle lung	22 by 14	1,000	70	4,000	23
				Left upper lung	3 by 3	1,000	70	4,000	24
				Left lower lung	5 by 5	1,000	70	4,000	24
II	54	F	Cancer, breast	Left lung	23 by 18	1,000	70	4,000	32
III	64	M	Cancer, lung	Left lung	25 by 18	1,000	100	4,000	27
IV	41	M	Cancer, lung	Left lung and left supraclavicular area	18 by 25	1,000	133	4,150	47
V	3½	M	Wilms' tumor	Right lung	13 by 10	250	50	1,850	12
				Left lung	13 by 10	250	50	1,850	9
VI	59	F	Cancer, ovary or uterus	Right lung	26 by 15	1,000	100	3,300	41
VII	21	M	Chondrosarcoma, pelvis	Right lung	23 by 15	1,000	70	3,000	17
VIII	51	M	Cancer, lung	Right lung	22 by 14	1,000	70	4,200	24
IX	69	F	Cancer, breast	Mediastinum	14 by 14	250	70	2,500	20
X	65	F	Cancer, breast	Right lung	16 by 13	1,000	70	2,000	13
XI	60	F	Cancer, breast	Mediastinum	14 by 10	1,000	70	3,000	15
XII	43	M	Synovioma, elbow	Left lung	10 by 10	1,000	70	2,600	15
				Right lung	8 by 8	250	70	1,700	24
XIII	58	F	Cancer, breast	Left lung	20 by 15	1,000	70	2,600	16
XIV	54	F	Cancer, breast	Mediastinum	16 by 13	250	70	2,500	35
XV	65	F	Cancer, esophagus	Esophagus	18 by 6.5 rotation	250	70	7,000	59

the roentgenographic signs of pneumonitis disappeared.

In 1954 two reports appeared in the literature on this subject. One was by Whitfield, Bond and Arnott.[5] They reported 4 cases, one of which received cortisone with temporary relief of symptoms and improvement in respiratory function; the other 3 cases received ACTH as a slow intravenous drip with no improvement in 1 patient and some improvement in 2 patients.

The other report was by Freidenberg and Rubenfeld.[4] Their series of 10 cases is the largest yet reported. In 9 of 10 cases cortisone was given for prevention of pneu-

TABLE II

DOSAGE AND RESULTS OF CORTISONE AND ACTH ON PREVENTION OF RADIATION PNEUMONITIS

Case No.	Roentgen Therapy			Cortisone			Appearance of Pneumonitis after Completion of Radiation (mo.)	Symptoms	Occurrence of Death from beginning of Radiation (mo.)	Autopsy
	Date Onset	Total Dose (r)	Total Days	Date Onset	Average Daily Dose (mg.)	Total Days				
I	Right lung 9/12/52	4,000	23	9/12/52	100	26	5	———	16	bilateral radiation pneumonitis and fibrosis
	Left lung 4/10/53	4,000	24	4/14/53	100 ACTH	20	4	———		
II	7/ 2/52	4,000	32	7/ 2/52	100	165	2½	Cough, dyspnea, cyanosis, fever	10½	radiation pneumonitis, fibrosis
III	6/26/52	4,000	27	6/26/52	100	60	4½	dyspnea, cough, hemoptysis	7	no autopsy
IV	1/17/52	4,150	47	2/11/52	200	30	1	dyspnea, cough	7	radiation pneumonitis, fibrosis
V	Right lung 2/10/53	1,850	12				2½	dyspnea, cough, fever, cyanosis	4	bilateral extensive radiation pneumonitis, fibrosis
	Left lung 2/10/53	1,850	9	3/12/53	25 q. o. d. (3½ yr. old child)	49	1½			
VI	11/13/52	3,300	41	12/ 8/52	100	37	1½	dyspnea, chest pain, cough, hemoptysis	22	no autopsy
VII	4/22/52	3,000	17	4/21/52	200–100 25	60	4	———	8	no autopsy
VIII	7/ 7/52	4,200	24	9/ 4/52	100	50	—	———	5	evidence of radiation pneumonitis

monitis. A dose of 100 mg. daily was administered one week after the commencement of radiation therapy to the lung, and was continued one to two weeks after the completion of irradiation. They reported that none of these cases developed radiation "fibrosis." Symptoms of pain, dyspnea and cough, presumably due to tumor, diminished in at least half of the cases. In 5 cases the follow-up after treatment was less than four months. In 1 case cortisone was given as a therapeutic measure for an existing radiation pneumonitis. There was symptomatic improvement but no marked change in the roentgen appearance of the lungs.

MATERIAL AND METHODS

Our presentation is based on the study of 15 cases. All of these patients received radiation therapy to the lung or mediastinum for either primary lung cancer or metastatic lesions within the thoracic cavity. All patients had frequent clinical evaluations and roentgenograms of the chest. The age of the patients varied from three and one-half to sixty-five years. Seven were males and 8 were females. Of the latter, 6 had carcinoma of the breast, 1 had carcinoma of the esophagus, and 1 had carcinoma of either the ovary or uterus. In the male group 3 had bronchogenic carcinoma, 1 had fibrosarcoma of the thigh, 1 had chondrosarcoma of the pelvis, 1 had synovioma of the elbow, and 1 had Wilms' tumor. The age, sex, pathologic process and factors of irradiation can be seen in Table 1. The half-value layer for the 1,000 kv. machine is 3.4 mm. Pb; for the 250 kv. beam is 2.0 mm. Cu.

TABLE III

DOSAGE OF CORTISONE AND ACTH AND THEIR EFFECTS ON EXISTING RADIATION PNEUMONITIS

Case No.	Cortisone		ACTH		Commencement of Therapy After Appearance of Pneumonitis (mo.)	Symptoms	Improvement of Symptoms	Improvement in Roentgen Appearance
	Average Daily Dose (mg.)	Duration in Days	Average Daily Dose (mg.)	Duration in Days				
I			100	20	½	none	—	none
II			200	101	0	dyspnea, cyanosis, cough, fever	temporary	yes
IV	100	11			3	none	—	none
V	150	8	100	3	1	dyspnea, cyanosis, cough, fever	none	none
VI	100–50	34			4	chest pain, dyspnea, cough, hemoptysis	temporary	none
IX	200	21			1	dyspnea, cough, fever	none	none
X	100	675			1	slight cough	improvement until death	none
XI	100	167			6	dyspnea, cough	improvement for a few months	slight
XII	100	55			0	dyspnea, cough	temporary	none
XIII	100	62			2½	chest pain, dyspnea, cough	temporary	none
XIV	50	110			4	dyspnea, cough	temporary	none
XV	300–100	30			1	dyspnea, cough fever	Improvement until death	slight

These 15 cases were divided into two groups: (A) In eight of the 15 cases cortisone or ACTH was given during and after the radiation therapy for the purpose of prevention of radiation pneumonitis and fibrosis. (B) In the remaining 7 cases cortisone or ACTH was given for treatment of existing pneumonitis. There were 5 cases from the first group (A) in which cortisone or ACTH was re-instituted as treatment after appearance of pneumonitis. Therefore, these 5 cases were also included in the evaluation of the therapeutic effects of cortisone and ACTH in radiation pneumonitis.

RESULTS

(A) *Effect of cortisone and ACTH in prevention of radiation pneumonitis.* In this group of 8 cases the dose to the lungs

FIG. 1. Case I. Metastatic fibrosarcoma, right lung. Before irradiation and cortisone therapy.

varied from 1,850 r to 4,150 r in nine to forty-seven days. The dose of cortisone in the 7 adult patients varied from 25 to 200 mg. daily for twenty to one hundred and sixty-five days. The three and one-half year old boy was given 25 mg. every other day for forty-nine days. The details of administration of cortisone or ACTH for each patient are given in Table II. All but one (Case VIII) developed roentgenographic evidence of pneumonitis one to five months after the completion of radiation therapy (Table II). Autopsies were obtained in 5 cases and all had evidence of radiation damage. In Case VIII, although no definite evidence of pneumonitis was noted on the chest roentgenograms, evidence of radiation pneumonitis was shown at autopsy five months after the institution of radiation therapy. In the 7 cases in which roentgenographic evidence of radiation pneumonitis developed, 5 had symptoms of cough and dyspnea (Table II).

(B) *Therapeutic effect of cortisone and ACTH on radiation pneumonitis.* Twelve cases were so evaluated. The details of cortisone institution or ACTH administration are presented in Table III. In 3 instances serial roentgenograms gave evidence of reduction in extent or severity of the pneumonitis. It was thought that this was due to the natural course of the pneumonitis rather than cortisone or ACTH effects. All of the patients developed evidence of pulmonary fibrosis (Table III).

REPORT OF CASES

CASE I. H.D. This twenty-nine year old white male had metastases in the right lung (Fig. 1) from a fibrosarcoma of the right thigh. Because of hemoptysis, roentgen therapy to the right lung was begun on September 12, 1952. A tumor dose of 4,000 r was delivered in twenty-three days using 1,000 kv. through 22 by 14 cm. anterior and posterior opposing fields. Cortisone 100 mg. daily was given during the period of irradiation. Subsequent roentgenograms of the chest showed development of new metastatic nodules in the left lung. The treated lesions in the right lung showed marked regression, and two smaller metastases apparently disappeared (Fig. 2). In March, 1953, five months after completion of irradiation of the right lung, roentgen evidence of extensive pneumonitis in that lung was present (Fig. 3). The patient, however, did not have any symptoms of this process.

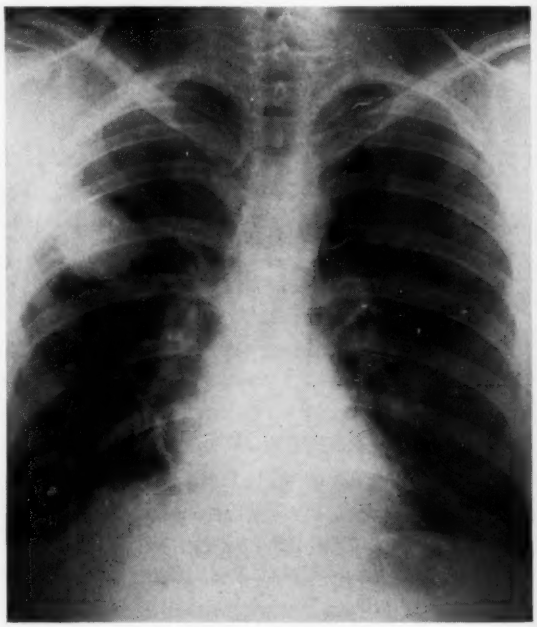

FIG. 2. Case I. Two months after irradiation, 4,000 r in twenty-three days to the right lung; marked regression of the tumor masses. New lesions appearing in the left lung.

In April, 1953, because of progression of the metastatic nodules in the left lung, roentgen treatment was instituted to two areas of the left lung, using a 3 by 3 cm. field and a 5 by 5 cm. field. Intramuscular ACTH gel 100 mg. daily was given concurrently. A tumor dose of 4,000 r was administered in three and one-half weeks. There was complete regression of the left upper lung nodule but only partial regression of the left lower lung lesion. In October, 1953, rapid regrowth of the secondaries was noted bilaterally. There was roentgenographic evidence of a small amount of fibrosis in the left lung. The patient died in January, 1954.

Case II. G. G. This fifty-four year old white female had a left radical mastectomy for an infiltrating duct carcinoma in 1950. In 1952 the patient complained of chest pain and dyspnea. Roentgenograms of the chest showed bilateral pulmonary and pleural metastases (Fig. 4). Roentgen therapy to the left hemithorax using 1,000 kv. was started on July 2, 1952. A tumor dose of 4,000 r was delivered in thirty-two days through 23 by 18 cm. anterior and posterior opposing fields. Cortisone therapy was instituted at the beginning of radiation therapy. The daily dose was 100 mg. for a period of six months.

The metastatic lesions in the irradiated lung showed continuous regression. Some regression of the tumor masses was thought to have occurred on the right side, also.

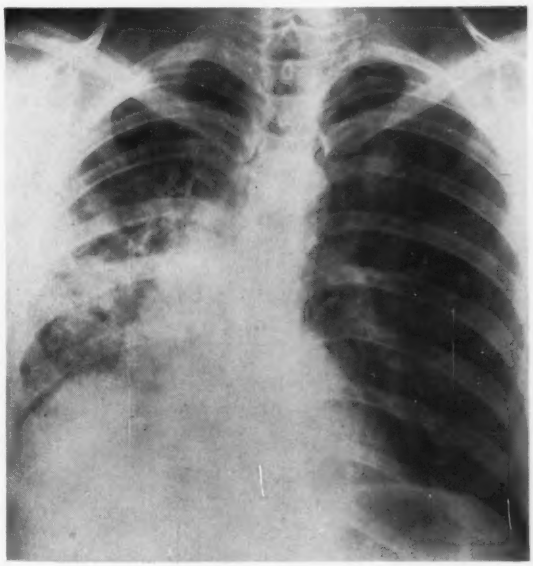

Fig. 3. Case I. Five months after completion of irradiation, pneumonitis in the right lung. Progression of lesions, left lung.

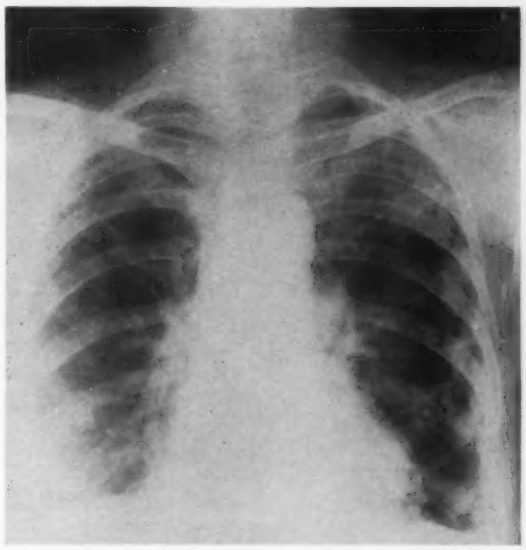

Fig. 4. Case II. Bilateral metastatic mammary carcinoma to lungs and pleurae. Before irradiation and cortisone therapy.

In October, 1952, early signs of radiation pneumonitis were detected in the roentgenograms. In January, 1952, the patient developed an acute episode of dyspnea, cyanosis and

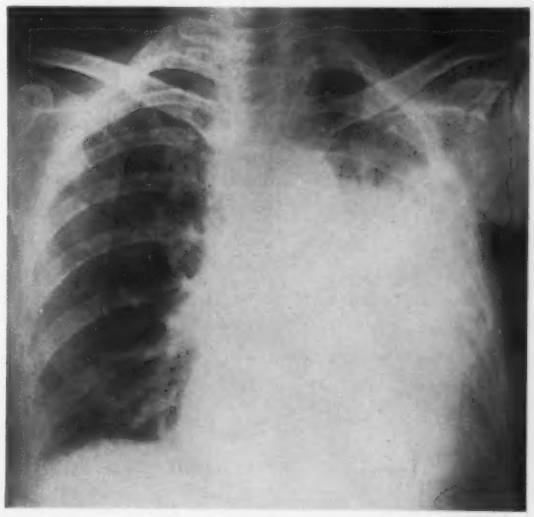

Fig. 5. Case II. In thirty-two days 4,000 r was given to the left hemithorax. Pneumonitis developed two and one-half months after completion of irradiation, reaching maximal reaction at five months, the time of this roentgenogram. Patient had cough, dyspnea, cyanosis and fever. She had been on cortisone 100 mg. daily for these six months. Cortisone was changed to ACTH.

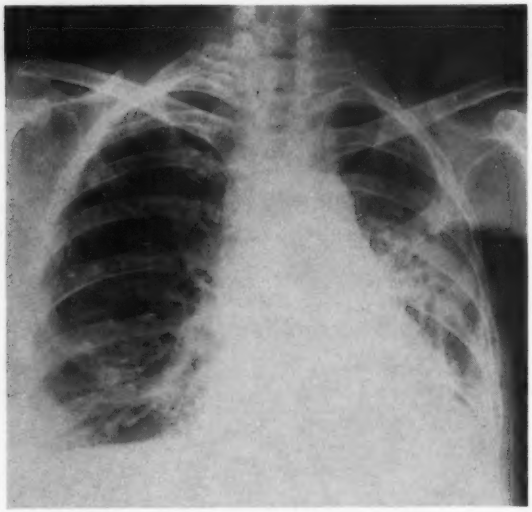

FIG. 6. Case II. Seven months after completion of irradiation. Acute inflammatory changes have subsided. Residual pneumonitis and fibrosis in the left lung. Patient became asymptomatic.

fever. Roentgenograms of the chest revealed an extensive pneumonitic process in the left lung (Fig. 5). The patient was immediately hospitalized. Under oxygen and penicillin therapy there was only slight improvement. Cortisone was discontinued and ACTH substituted. A daily dose of 200 mg. was given intramuscularly for three and one-half months. The dyspnea improved considerably and the patient became asymptomatic. Attempts to reduce the dose of ACTH to 100 mg. resulted in recurrence of symptoms. She began to develop Cushing's syndrome. Roentgenograms of the chest showed clearing of the acute penumonitic process. Residual infiltration and fibrosis was present (Fig. 6).

Unfortunately this patient died suddenly of a pulmonary embolism. Autopsy showed a large thrombus in the right pulmonary artery, fibrosis and atelectasis of the left lung, secondary to radiation.

CASE III. J.M. This sixty-four year old male developed increasing cough and intermittent left chest pain in March, 1952. When first seen at the Memorial Hospital in June, 1952, the patient had a left pleural effusion. Cytologic study of the pleural fluid revealed malignant cells. The primary tumor was thought to be in the left lung. Roentgen therapy using 1,000 kv. to the left chest was instituted. A tumor dose of 4,000 r was delivered in four weeks. Cortisone 100 mg. daily was given concurrently and continued for one month after the completion of radiation therapy. There was subjective and objective improvement after the completion of irradiation which lasted about four and one-half months. Then evidence of pneumonitis on the irradiated side was noted on the roentgenogram.

The patient developed cough, dyspnea and hemoptysis, with death occurring in January, 1953. No autopsy was obtained.

CASE IV. J.N. This forty-one year old white male had an anaplastic epidermoid carcinoma of the left upper lung with metastases to the cervical lymph nodes on both sides. His chief complaints were cough, dyspnea, chest pain and hoarseness of several months' duration. On January 10, 1952, he was given HN_2 intravenously, 0.4 mg./kg. body weight. Irradiation to the left lung and neck was started one week later using 1,000 kv. The tumor dose was 4,150 r in forty-seven days. During the course of irradiation 200 mg. of cortisone was administered daily for a month. After the completion of the therapy there was marked regression of the tumor masses.

In April, 1952, one month after the completion of the radiation therapy, signs of pneumonitis in the left lung were seen in the roentgenogram. The pneumonitis became more extensive in June, 1952. The patient began to have increasing dyspnea and cough. Cortisone was re-instituted but there was no response. His neoplastic disease also progressed rapidly and he died on August 21, 1952. Autopsy showed anaplastic epidermoid carcinoma of the left upper lobe with metastases to lymph nodes and many visceral organs. There was radiation pneumonitis and fibrosis in the left lung.

CASE V. J.P. This three and one-half year old boy had bilateral pulmonary metastases from a Wilms' tumor (Fig. 7). A left nephrectomy followed by irradiation of the operative area was completed four months prior to the discovery of pulmonary metastases.

When first seen at the Memorial Hospital in February, 1953, administration of 6-mercaptopurine, 50 mg. daily, and roentgen therapy to the lungs was planned. The right lung was irradiated first, using 250 kv. roentgen therapy and two opposing fields of 13 by 10 cm. A tumor dose of 1,850 r was given in twelve days. In March, 1953, there was almost complete clear-

ing of the right lung (Fig. 8). Irradaition of the left lung was therefore instituted using the same factors. A similar tumor dose was delivered in nine days and at this time cortisone 25 mg. every other day was also given. In April, 1953, the metastatic lesions in both lungs had completely disappeared. At the end of April, 1953, a roentgenogram of the chest showed evidence of pneumonitis in the right lung which had been treated first. The patient began to run a low grade fever. In May, 1953, evidence of pneumonitis was also seen in the left lung (Fig. 9). The child became very ill. There was increasing cough, dyspnea, and cyanosis. The course was downhill despite energetic treatment, including digitalization, antibiotics, oxygen, ACTH and hydrocortisone. Death occurred on June 4, 1953. Autopsy showed bilateral extensive pneumonitis and pulmonary fibrosis. No residual tumor was noted in the lungs.

CASE VI. S.C. This fifty-nine year old white female had pulmonary and pleural metastases in the right hemithorax from either an ovarian or uterine primary cancer. She was given intrapleural Au^{198} followed by external irradiation of the right hemithorax. A tissue dose of 3,300 r in forty-one days was delivered with the 1,000 kv. machine. Cortisone 100 mg. daily was instituted concurrent with the external irradiation. One and one-half months after the completion of the radiation therapy, the patient developed evidence of pneumonitis which was complicated by two episodes of secondary pulmonary infection. Her chief symptoms due to the pneumonitis were cough, dyspnea, chest pain and hemoptysis. The roentgenographic appearance of the right chest after the development of pneumonitis showed very little change until about a year later, when there seemed to be an increase in the fibrotic elements. At the same time, several metastatic nodules had appeared in the left lung. Cortisone was re-instituted with a daily dose of 100 mg. and then reduced to 50 mg. The treatment was continued for a month. Although there was symp-

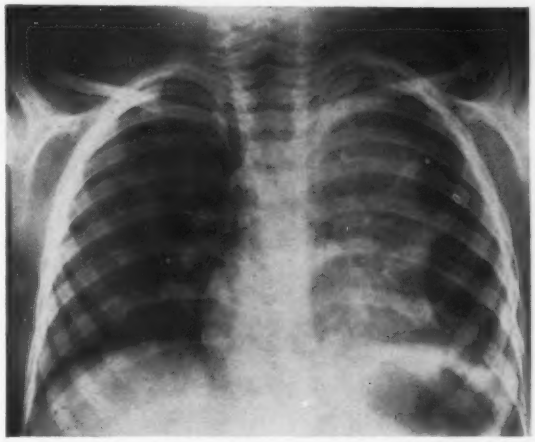

FIG. 8. Case v, One-half month after administration of 1,850 r in twelve days to the right lung the lesions almost completely disappeared. The metastases in the left lung had progressed considerably. In nine days 1,850 r was given to the left lung Cortisone therapy begun.

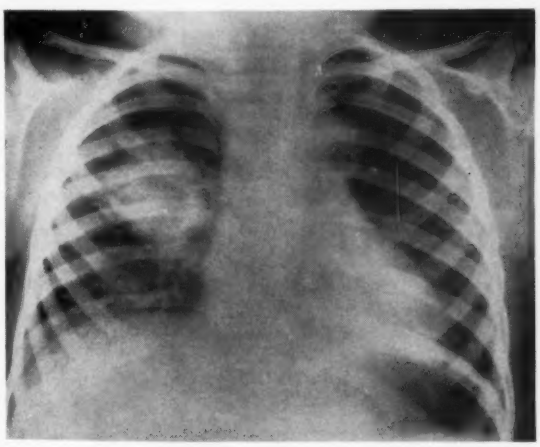

FIG. 7. Case v. Three and one-half year old boy with bilateral metastates in the lungs, from Wilms' tumor.

FIG. 9. Case v. Bilateral pneumonitis two and one half months after irradiation of the right lung and one and one-half months after irradiation of the left lung. The child died despite ACTH, antibiotics and supportive therapy.

tomatic improvement of cough and dyspnea, there was no roentgenographic evidence of clearing of the pneumonitis. The patient's course was rapidly downhill and she died twenty-two months after the beginning of radiation therapy. No autopsy was obtained.

CASE VII. T.C. This twenty-one year old white male came to the Memorial Hospital in April, 1952, with a history of a mass in his right hip associated with pain of six months' duration. Biopsy of this mass revealed a spindle cell sarcoma. Roentgenograms of the chest showed bilateral pulmonary metastases. Because of cough and a mass in the right lower lung, roentgen therapy of that lung was begun on April 22, 1952. Using 1,000 kv. and two opposing fields 23 by 15 cm. a tumor dose of 3,000 r was delivered in seventeen days. Cortisone therapy was instituted one day prior to the radiation therapy. The daily dose was 200 mg. for three weeks, 100 mg. for four weeks and 25 mg. for ten days. The right lung mass became smaller and the patient became asymptomatic. In view of the response, radiation treatment was also given to the huge primary lesion.

In September, 1952, four months after completion of irradiation of the lung, evidence of pneumonitis was seen in the roentgenogram. In December, 1952, there was evidence of pulmonary fibrosis at the irradiated site. There was no symptom referable to this process. The patient's disease progressed rapidly and he died at the end of December, 1952.

CASE VIII. R.W. This fifty-one year old white male had an oat cell carcinoma of the right lung with metastases to the mediastinal and supraclavicular lymph nodes. His chief complaints were cough and weakness of three months' duration. On June 20, 1952, he was given an intravenous dose of HN_2, 0.4 mg./kg. body weight. On July 7, 1952, roentgen therapy was instituted. Using the 1,000 kv. machine and 70 cm. target skin distance a tumor dose of 4,200 r was delivered to the mediastinum in twenty-four days through two opposing fields of 22 by 14 cm. One month after the completion of radiation therapy, a course of cortisone was given with a daily dose of 100 mg. for fifty days. The patient did well for a few months. There was no definite evidence of pneumonitis on follow-up roentgenograms. On December 4, 1952, five months after the institution of radiation therapy, the patient died suddenly of a cerebral hemorrhage. Autopsy showed oat cell carcinoma of the right lung with metastases to many distant organs. There was evidence of radiation pneumonitis.

CASE IX. C.N. This sixty-nine year old white female had dyspnea due to mediastinal metastases from carcinoma of the breast. Using 250 kv. and 14 by 14 cm. anterior and posterior fields, a tumor dose of 2,500 r in twenty days was given to the mediastinum in November, 1953. The patient had complete symptomatic relief two weeks after the completion of the therapy. Roentgenogram taken one month after the completion of treatment showed marked regression of the enlargement of the mediastinum.

In February, 1954, two and one-half months after the completion of the irradiation, both lungs showed patchy infiltration consistent with radiation pneumonitis. Two weeks later the patient developed cough, dyspnea, and low grade fever. Cortisone, 200 mg. daily, was started. Symptoms and roentgenographic signs became worse. The patient died in March, 1954, two and one-half months after the onset of radiation pneumonitis and three weeks after the institution of cortisone therapy. No autopsy was obtained.

CASE X. C.B. This sixty-five year old white female had a bulky ulcerated carcinoma of the right breast with metastases to the right axilla and the lungs. Estrogen administration and roentgen therapy to the right lung were started on April 10, 1952. Using 1,000 kv. roentgen rays, a tumor dose of 2,000 r in thirteen days was delivered to the right lung through one anterior and one posterior opposing field 16 cm. by 13 cm. This was followed by irradiation of the right breast, axilla and supraclavicular areas through three tangential fields. The tumor dose was 3,200 r in twenty-three days. The breast mass became much smaller and the ulcer completely healed.

In August, 1952, three and one-half months after the completion of the irradiation, evidence of radiation pneumonitis was noted on the roentgenogram. The patient had only a slight cough. In October, 1952, cortisone therapy was instituted, 300 mg. daily for three days, 200 mg. daily for three days and 100 mg. daily continued until the sudden death of an unknown cause in August, 1954. There was no

significant interval change in the appearance of the radiation effect in the lung during this period of two years. No autopsy was obtained.

CASE XI. F.W. This sixty year old white female developed metastases to the lacrimal duct of the left eye, skin, both lungs and mediastinum five years after a right radical mastectomy and postoperative irradiation for an infiltrating duct carcinoma of the breast. When first seen at the Memorial Center in March, 1953, she was complaining of cough. The patient was started on progynon and at the same time radiation therapy to the mediastinum and the right lung root was given. Using 1,000 kv. roentgen rays, a tumor dose of 3,000 r was delivered in fifteen days through anterior and posterior opposing fields, 14 by 10 cm. Several skin nodules were irradiated with low voltage roentgen rays. Shortly after the completion of radiation therapy, the patient's cough had diminished and the roentgenogram of the chest showed some regression of the mediastinal and pulmonary infiltration. Two months later roentgenographic evidence of radiation pneumonitis appeared and the patient experienced cough and dyspnea. Although the roentgenograms of the chest had already shown gradual resolution of the pneumonitis, she was started on cortisone therapy six months after the appearance of pneumonitis because of persistent cough and dyspnea. The initial dose was 300 mg. daily for three days and then she was maintained on 100 mg. daily for five and one-half months. The roentgenograms of the chest showed further clearing of the pneumonitis with appearance of pulmonary fibrosis in some areas. The patient had some improvement of symptoms for a few months. She is still alive. When last seen, February, 1954, cough was still a distressing complaint. There has been no change in the pulmonary picture.

CASE XII. P.N. This forty-three year old white male was given 1,000 kv. roentgen ray therapy to the left lower lung in January, 1954, for metastases from a synovial sarcoma of the right forearm. A tumor dose of 2,600 r was administrated in fifteen days through 10 by 10 cm. fields. The symptoms prior to the treatment were slight cough and dyspnea. In February, 1954, another course of roentgen therapy was given to the right hilar region for a metastatic mass. This time 250 kv. roentgen rays were used. A tumor dose of 1,700 r was delivered in twenty-four days through anterior and posterior opposing fields, 8 by 8 cm. In May, 1954, four months after the first course of radiation therapy and three months after the second course, the patient's dyspnea became markedly accentuated. Roentgenogram of the chest showed definite evidence of pneumonitis in the left lower lung and possible pneumonitis in the right hilar area. Treatment with cortisone 100 mg. daily was instituted and continued for about two months. There was a temporary improvement of the dyspnea for two weeks. Then the patient's condition steadily deteriorated. The pulmonary metastases had spread more widely, cough and dyspnea became worse. The patient died in August, 1954. There was no roentgenographic evidence of diminution in the extent or degree of pneumonitis.

CASE XIII. F.H. This fifty-eight year old white female was given radiation therapy in September, 1952, to the left lower lung for metastases from carcinoma of the breast. The tumor dose was 2,600 r in sixteen days through 20 by 15 cm. anterior and posterior opposing fields. There was marked regression of the size of the metastatic nodules in the irradiated area three weeks after the completion of the roentgen therapy. In November, 1952, seven weeks after the completion of treatment, the patient developed marked dyspnea, cough and chest pain. Roentgenograms of the chest revealed pneumonitis in the irradiated lung. In January, 1953, cortisone therapy was instituted. A daily dose of 100 mg. was continued for sixty-two days. There was symptomatic improvement but no change in the roentgenographic appearance. The patient died of generalized metastases in July, 1953. No autopsy was obtained.

CASE XIV. M.M. This fifty-four year old white female had a right radical mastectomy for carcinoma of the breast in September, 1951. In September, 1953, she developed dysphagia and left vocal cord paralysis. Roentgenogram of the chest showed enlargement of the mediastinal and hilar lymph nodes and evidence of pulmonary metastases. The patient was put on testosterone and radiation therapy in November, 1953. A tumor dose of 2,500 r to the mediastinum in thirty-five days was delivered with 250 kv. roentgen rays. The size of the anterior and posterior fields was 16 by 13 cm. Shortly after the completion of treatment roent-

gen evidence of pneumonitis sharply confined to the irradiated area was seen. Although there was some regression of the pneumonitis in a period of four months, the patient's cough and dyspnea became progressively worse. Therefore, cortisone treatment was instituted. The daily dose varied from 100 mg. to 25 mg. Treatment was continued for almost four months. There was little symptomatic improvement. However, as soon as the cortisone was withdrawn, the symptoms worsened.

CASE XV. C.G. This sixty-five year old white female was irradiated for anaplastic epidermoid carcinoma of the esophagus in December, 1953 with 250 kv. rotational radiation treatment. Field size was 18 by 6.5 cm. and the tumor dose was 7,000 r in fifty-nine days. Two weeks after the completion of treatment, the patient developed cough, fever and dyspnea. Roentgenogram of the chest showed pneumonitis in both lung fields near the hilar areas. Antibiotics were given. Fever and cough subsided in about one week, but dyspnea persisted. In April, 1954, the dyspnea was only slightly improved. Therefore, the patient was started on cortisone therapy. The initial dose was 300 mg. daily and then the patient was maintained on 100 mg. daily for an overall period of one month. There was some diminution in the dyspnea and slight clearing of the pneumonitis on roentgenographic examination. Unfortunately this patient died of generalized metastases in July, 1954, five months after the rotational therapy and three months after the cortisone therapy. No autopsy was obtained.

DISCUSSION

The evaluation of the effects of ACTH and cortisone on radiation pneumonitis is a difficult problem. The development of pneumonitis and pulmonary fibrosis after irradiation varies widely as to its incidence, time of appearance, extent of involvement and persistence. These variables, together with the roentgenographic differential diagnosis of radiation pneumonitis, have been discussed by some of the authors of this paper.[2]

Symptoms due to pneumonitis likewise vary a great deal. Some patients with relatively extensive pneumonitis do not have symptoms and some patients have symptoms which may subside spontaneously without treatment. Also the roentgenographic signs of pneumonitis may disappear without specific treatment. Therefore, in the evaluation of the effect of any protective or therapeutic means on radiation pneumonitis, all these factors have to be considered.

The cases reported in the literature with objective improvement after ACTH or cortisone treatment as indicated by roentgenographic signs or by respiratory function tests[1,3,5] may perhaps have improved as the result of the natural course of radiation pneumonitis. In Freidenberg and Rubenfeld's 9 cases,[4] although beneficial effects in prevention of radiation pneumonitis were reported, the majority of cases were followed less than four months and no case was followed more than six months. To us the follow-up periods seem too short, and do not permit a definite conclusion to be drawn. It is known that roentgenographic signs of pneumonitis may develop as late as four or five months after completion of radiation therapy. Therefore, it is probably not justifiable to conclude that ACTH or cortisone offers protection against radiation pneumonitis on the basis of periods of observation of less than six months.

The improvement of the symptoms of radiation pneumonitis after the use of ACTH or cortisone may be nonspecific since these substances tend to suppress symptoms. In this series of 15 patients, it is felt that there was improvement in symptoms in some cases, particularly in Cases II and XIV in which symptoms of cough and dyspnea recurred with attempted reduction or withdrawal of the hormone. Case II finally developed Cushing's syndrome.

There is no definite evidence of prevention or alleviation of the objective signs of radiation pneumonitis by roentgenographic studies. We were able to obtain 5 autopsies in the 8 cases in which ACTH or cortisone was given for the purpose of preventing pneumonitis. All showed pneumonitis and fibrosis. Case VIII was thought to be free

of roentgenographic signs of radiation pneumonitis four months after completion of radiation therapy. However, evidence of radiation pneumonitis was noted at autopsy.

Case v is particularly worth mentioning. This three and one-nalf year old boy received 1,850 r in twelve days to the right lung, followed one month later by 1,850 r to the left lung in nine days. Cortisone was given during and after the second course of radiation therapy. This child developed severe bilateral pneumonitis and fibrosis and died. Cortisone in the amounts given did not protect the lungs from pneumonitis or pulmonary fibrosis. Each lung was treated with almost the same roentgen factors, one concurrently with cortisone treatment and one without. The development of pneumonitis and fibrosis was the same in both lungs. An attempt was made also to treat this child's pneumonitis with hydrocortisone and ACTH which also failed to save his life.

It may be that the dosage of cortisone was inadequate and that larger doses would have helped him. The fact remains that cortisone in the amounts given did not prevent pneumonitis.

Case II developed severe pneumonitis in the left lung despite continuous cortisone therapy of 100 mg. daily for six months, beginning at the commencement of radiation therapy. This patient had acute symptoms of dyspnea, cyanosis and fever. Cortisone was changed to ACTH. Symptoms improved and the acute pneumonitic process in the left lung gradually changed to a chronic pneumonitis with fibrosis which lasted to the time of her death. In this case cortisone certainly did not prevent the pneumonitis. ACTH may have helped the patient during the phase of the respiratory distress.

In conclusion, the value of ACTH and cortisone in the management of radiation pneumonitis is at best relief of symptoms in some cases. We have found no objective evidence that either of these hormones prevented the occurrence or definitely alleviated the roentgenographic signs of radiation pneumonitis or fibrosis.

SUMMARY

1. A study of the effects of ACTH and cortisone on radiation pneumonitis in 15 cases is presented.

2. A brief review of the reports in the literature is given.

3. No definite evidence of protection against development of pneumonitis by the use of ACTH or cortisone was seen in 8 cases.

4. No appreciable evidence of improvement in roentgenographic signs of radiation pneumonitis was found in 12 cases of this series.

5. ACTH and cortisone alleviated symptoms caused by radiation pneumonitis in some of the cases.

6. In evaluation of effects of any therapeutic agent on radiation pneumonitis, the importance of considering the variability of the natural course of radiation pneumonitis is stressed.

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THE THERAPEUTIC USE OF SINGLE DOSES OF TOTAL BODY RADIATION*†

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RADIATION therapy and chemotherapy are recognized as having equivalent or complementary roles in the treatment of certain types of cancer. In general, radiation has been restricted to the treatment of relatively localized manifestations, and chemotherapy has been used when the disease is more widely disseminated. There has been limited use of total body irradiation in the treatment of generalized neoplastic disease. In the Heublein technique[8,11] low intensity, continuous irradiation was used to administer doses up to 450 roentgens in three weeks. Hempelmann *et al.*,[6] writing on the acute radiation syndrome, noted that 100 r of 200 kv. roentgen rays could be delivered to the entire body of the patient without causing symptoms of any sort. Recently, Osgood and Seaman[12] have advocated a "titration technique" in the treatment of leukemia in which doses of 10–25 r were given to the whole body at regularly spaced intervals. In a scrupulous effort to avoid radiation sickness and bone marrow depression, a conventional technique employing total body irradiation for the treatment of polycythemia utilizes doses of 25 r repeated to a total of 300 r in three weeks. From these different techniques, using varying formulae of intensity, dose, and time, it is difficult to assess the tolerance to whole body irradiation.

Perhaps the most extensively employed chemotherapeutic agent has been nitrogen mustard, methyl bis (beta chloroethyl) amine (HN_2). This agent has been used in almost every form of malignant disease and in some benign conditions such as rheumatoid arthritis.[4] It has become the standard form of therapy for generalized Hodgkin's disease. In accepted clinical doses, nitrogen mustard produces a sharp systemic reaction and the patient is heavily sedated before treatment to control nausea and vomiting. Hematopoietic depression is constant, and severe leukopenia and thrombocytopenia is a recognized hazard of repeated courses. These toxic side effects have not been a deterrent to common use although they exceed the severity of radiation sickness.

In 1950 Gellhorn and Collins[5] undertook a comparative study of two groups of patients with Hodgkin's disease, one of which had received radiation and nitrogen mustard in alternating therapeutic courses, and the other radiation therapy alone. It could not be shown that the addition of nitrogen mustard to the therapy regimen increased survival time but the drug was regarded as a useful adjunct to the extent that it reduced the time under treatment and the amount of radiation required. If nitrogen mustard did not increase survival time beyond that obtained with radiation therapy alone, its only purpose was to offer the convenience of a systemic approach to treatment. It seemed possible that higher doses of total body irradiation might offer equal benefit with side effects of less severity. Phillips *et al.*[13] had studied the application of massive doses of radiation to liver for metastatic disease. Court Brown[3] had reported observations on symptoms associated with single therapeutic doses of roentgen radiation to large portions of the body, and to the whole body.

In a previous report the tolerance to total body irradiation was compared with the effects of nitrogen mustard and triethylene

* From the Department of Radiology, Baylor University College of Medicine, and the Jefferson Davis Hospital, Houston, Texas. Presented at the Thirty-sixth Annual Meeting, American Radium Society, Hot Springs, Virginia, March 14–16, 1954.
† This work was aided in part by the Medical Research and Development Board, Office of the Surgeon General, Department of the Army, Contract No. DA-49-007-MD-428.

melamine.[10] Total body irradiation in single doses up to 150 r was less depressing for hematopoiesis and patients were free of malaise that was constantly associated with these drugs. These observations suggested that a therapeutic effect of total body irradiation might be sought in patients having disseminated disease ordinarily treated by a variety of chemotherapeutic agents.

In the present series of patients, dose has been expressed in roentgens on skin and measurements were made with a Victoreen chamber on the surface of a pressdwood phantom at treatment distance. Court Brown and Mahler[2] reported their series of single exposures to radiation in terms of energy absorbed or integral dose. There was some necessity for this in that their patients received treatment to varying portions and proportions of the body, and dose in roentgens would have no direct correlation with tolerance of the individual to radiation. For purposes of duplication, dose on skin represents the simplest expression of exposure to radiation. Boden and Cohen[1] have called attention to variations that exist in measuring dose in different institutions and it appears that no accuracy would be gained in the assumptions and calculations necessary for determining integral dose for total body irradiation.

In addition to the usual blood examinations, radioactive iron tracer studies were carried out because of the work of Hennessy and Huff[7,9] indicating a quantitative relation between the utilization of injected iron for hemoglobin production, and dose of total body irradiation, in rats. The half time of disappearance of radioiron from the blood is normally one to two hours for humans. Prolongation of the half time indicates decreased hemoglobin formation and may be useful as an early and sensitive index of change in guiding further therapy.

	Initial	*Low*	*Final (11 mo.)*
Hb.	11.9 gm.	7.6 gm. @ 5 wk.	11.0 gm.
R.B.C.	4,300,000	1,700,000 @ 5 wk.	3,800,000
W.B.C.	29,000	4,000 @ 8 wk.	10,000
Platelets	240,000	110,000 @ 8 wk.	148,000
Iron turnover half time	1.3 hr.	4.2 hr. @ 23 days	0.4 hr.

REPORT OF CASES

CASE I. B.L. (AR-8422) A male, aged seventy-three, developed generalized lymphadenopathy in November, 1951, and a diagnosis of "lymphoma" was made by biopsy. Treatment was withheld because of lack of symptoms. In March, 1953, the patient was admitted to the hospital because of 20 pounds weight loss, pain in left shoulder, and edema of left upper extremity. There was extensive lymphadenopathy with nodes as large as 5 cm. in diameter; liver extended 5 cm. below the costal margin.

On March 23, 1953, the patient received 75 r (skin dose) total body irradiation anteriorly and 75 r posteriorly (250 kv., constant potential, half-value layer 2.3 mm. Cu, target skin distance 360 cm.). In the first forty-eight hours the patient was anorexic but there was no nausea, vomiting or diarrhea. On the third day the patient's appetite returned and the lymph nodes began to diminish in size. On May 12, 1953, he was discharged from the hospital and returned to work. Later in the month he received 600 r tissue dose to the mediastinum in eight days on an out-patient basis. In December, 1953, in another city, he underwent partial gastric resection for ulcer of the lesser curvature. At present he is convalescing satisfactorily.

Laboratory data during the period associated with total body irradiation were as follows:

Differential white cell count became normal at eight weeks.

CASE II. W.D. (AJ-6024) A seventy-two year old white male was admitted for repair of inguinal hernia and was discovered to have a white blood cell count of 155,000. The differential white cell count was consistent with chronic myelogenous leukemia. Liver and spleen were palpably enlarged. The blood pressure was 200/90. He had lost 20 pounds in

weight in the past year. On June 24, 1953, he received 150 r (skin dose) total body irradiation to the anterior aspect of body (250 kv., half-value layer 2.3 mm. Cu, target skin distance 360 cm.). There was mild anorexia on the following morning but his appetite was normal by noon. There was no nausea, vomiting or malaise. Liver and spleen gradually diminished in size and were no longer palpable after two weeks.

Laboratory data during treatment and follow-up were as follows:

	Initial	*Low*	*Final (8 mo.)*
Hb.	10.1 gm.	7.5 gm. @ 4 wk.	11.0 gm.
R.B.C.	3,800,000	2,900,000 @ 4 wk.	3,100,000
W.B.C.	193,000	11,000 @ 3 mo.	98,000
Platelets	265,000	225,000 @ 1 wk.	216,000
Iron turnover half time	0.6 hr.	2 hrs. @ 1 day	1.5 hr.

Differential white cell count became normal at three months.

CASE III. J.B.C. (AX-7573) A fifty-one year old white male was admitted to the hospital on September 10, 1953, with a biopsy diagnosis of multiple myeloma. He had been paraplegic and incontinent of urine and feces for three weeks; he had developed a large sacral decubitus ulcer, his general condition was poor and he complained of severe dorsal and lumbar back pain. He was placed on a Foster frame and daily care was given to the decubitus ulcer, which showed slow improvement.

On September 15 he was given 200 r (skin dose) total body irradiation (250 kv., peak, half-value layer 2.3 mm. Cu, target skin distance 360 cm.). There was mild nausea of one day's duration; there was no vomiting. Because there was only partial loss of tactile sensation accompanying the motor paralysis, the total body irradiation was followed two weeks later by local roentgen therapy to the spine. A tissue dose of 675 r was delivered in ten days to vertebral bodies from C-4 to S-1. No change was detected in the neurologic findings; however, narcotic requirements for pain were considerably less than before treatment. The patient's condition gradually deteriorated and he died on Oct. 28, 1953. No autopsy was obtained.

Laboratory data during the period associated with total body irradiation were as follows:

	Initial	*Low*	*Final (6 wk.)*
Hb.	11.0 gm.	5.7 gm. @ 4 wk.	7.5 gm.
W.B.C.	8,500	4,050 @ 5 wk.	5,500
Platelets	240,000	220,000 @ 4 wk.	250,000

There was no change in differential white blood cell count.

CASE IV. O.B. (Y-13361) This white female, aged fifty-eight, gave a six year history of backache radiating to the legs. In April, 1948, she received roentgen therapy to a destructive lesion in the body of the second lumbar vertebra with diminution of pain. In 1951 a second course of therapy was given to this area, and in January, 1952, a third course. On Feb. 23, 1952, a spinal fusion was carried out and a diagnosis of multiple myeloma was established. Further lesions developed in skull and ribs. On Oct. 26, 1953, the patient, now a paraplegic with complete destruction of the body of the third lumbar vertebra, and constant severe back pain, was transferred from another hospital for total body irradiation. On Nov. 11, 1953, with patient turned on her side in bed, she received 200 r (skin dose) to back (250 kv., half-value layer 1.8 mm. Cu, target skin distance 365 cm). There were two episodes of vomiting without nausea at four and six hours after treatment and minimal nausea but no further vomiting on the first and second post-treatment days. From the third treatment day there were no further symptoms of nausea and moderate pain relief was noted. Pain began to become more severe again after five weeks. On Dec. 16, 1953 (five weeks) the patient received another 100 r (skin dose) to the back under the same conditions as previously. There were no symptoms of nausea or vomiting, and again there was some reduction in back and leg pain. Pain was relieved for about one month and then recurred with the same severity as before treatment. For this reason a cervical cordotomy was planned, but the patient died at operation on Jan. 28, 1954.

An autopsy was performed. The tumor that had received intensive local irradiation showed

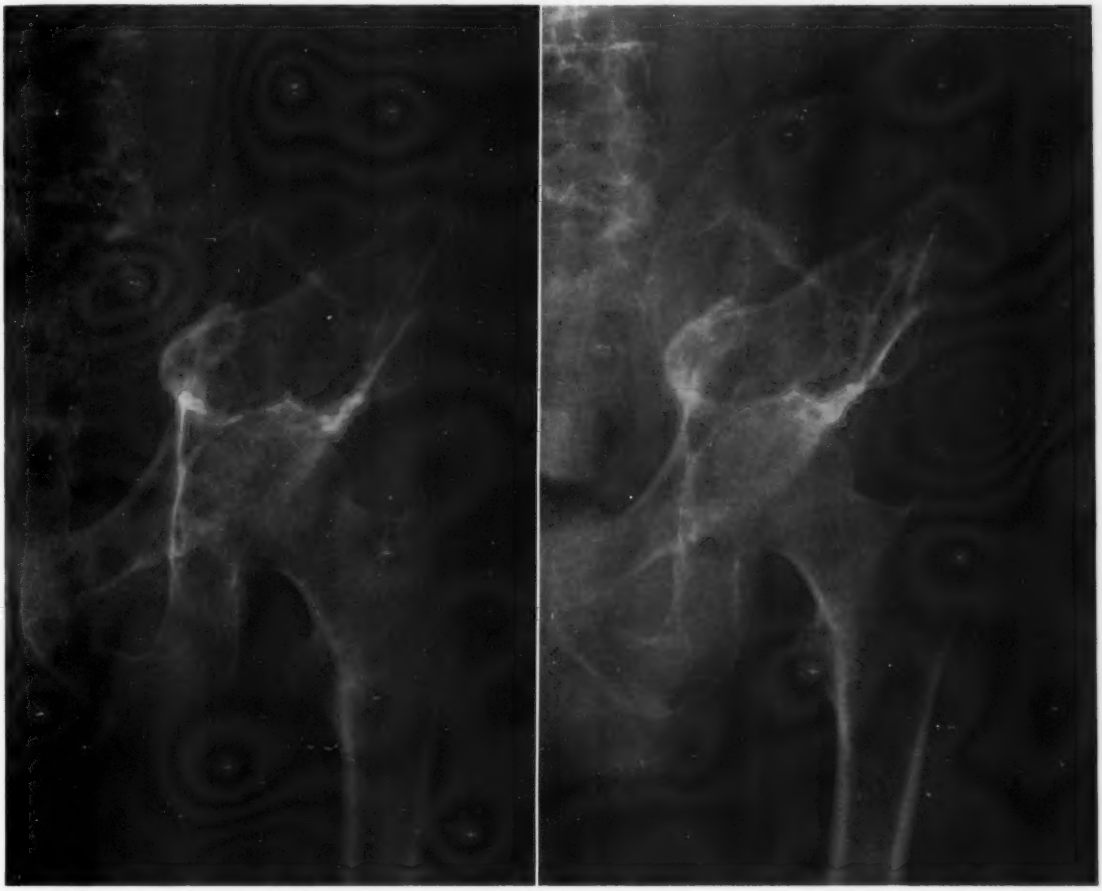

Fig. 1. Case v. J.C. The pelvis shows extensive involvement by multiple myeloma with biopsy defect and pathologic fracture involving the left ilium. The bone lesions showed no progress in the eight months following treatment.

histopathologic changes consistent with this treatment. Normal tissues that had been subjected to total body irradiation showed no gross or microscopic effects of such irradiation.

Laboratory data during the treatment period showed maximal depression from the 200 r dose.

	Initial	*Low*	*Final (7 wk.)*
Hb.	12.5 gm.	8.7 gm. @ 3 wk.	8.9 gm.
R.B.C.	4,000,000	2,700,000 @ 3 wk.	2,800,000
W.B.C.	11,000	2,600 @ 3 wk.	5,200
Platelets	150,000	50,000 @ 5 wk.	92,000

The differential white blood cell count at three weeks showed an increase in lymphocytes but the absolute lymphocyte count remained approximately constant.

Case v. J.C. (AX-5284) A white male, aged thirty-five, had suffered a fracture of cervical spine in an accident three years previously and extensive lesions of multiple myeloma were discovered at that time. A year later the diagnosis was confirmed by biopsy. Except for a gradual weight loss of 45 pounds, the patient remained well, subjectively, until four months before admission. From this time he was confined to bed by severe back pain and increasing weakness. Roentgenograms showed compression fractures of several vertebral bodies and he was transferred to the hospital on a Stricker frame. On July 22, 1953, he received 200 r (skin dose)

total body irradiation (250 kv., half-value layer 2.3 mm. Cu, target skin distance 400 cm.). Immediately after treatment he vomited once without nausea. He ate his noon day meal two hours later and had no further reaction. Pain relief was evident the day following treatment, and by the third day appetite was improved. On Aug. 13, 1953, a second dose of 200 r, under the same conditions as the first, was administered. This time there was no nausea or vomiting and there were no new complaints. One week later he was completely relieved of back pain and was up and about the ward voluntarily. His only complaint was of pain in feet and ankles. There were no roentgen changes evident in the bones of this area and the pain apparently was due to ambulation after five months in bed. He received five transfusions of 500 cc. each during September and was then discharged home. He has received no further treatment and now talks hopefully of returning to work (Fig. 1).

Laboratory data during this period were as follows:

	Initial	*Low*	*Final (8 mo.)*
Hb.	8.3 gm.	6.0 gm. @ 5 wk.	11.0 gm.
R.B.C.	3,800,000	1,700,000 @ 5 wk.	3,200,000
W.B.C.	6,000	550 @ 5 wk.	8,250
Platelets	295,000	13,000 @ 6 wk.	210,000
Iron turnover half time	0.5 hr.	1.0 hr. @ 3 wk.	0.8 hr.

The differential white cell count at five weeks showed a doubling in the percentage of lymphocytes.

For both radiation therapy and chemotherapy, the ultimate effects are mediated by intracellular chemical changes. For this reason the two may be compared on terms of tolerance of the individual response of the disease, and factors governing their role in application.

Tolerance to radiation does not lend itself to ready measurement. In Court Brown's[3] series of 60 patients, he was able to define three phases of radiation sickness: (1) the latent period extending from the time of treatment to the onset of symptoms; (2) a period of acute disturbance lasting from one and one-half to four hours after the onset of symptoms; (3) recovery period extending as long as four or five days. The length of the latent period was inversely proportional to the period of acute symptoms and was used as an index of severity of reaction. In the patients presented here, a pattern of symptoms was not apparent; nausea and vomiting were inconstant and their condition before treatment was such as to mask any minor degree of weakness or lethargy. From a symptomatic point of view, the reaction to single doses up to 200 r was less than would be anticipated with conventional doses of nitrogen mustard, and the hematopoietic depression was acceptable as compared with this agent.

The response of the patients' disease can only be considered as indicative that total body irradiation in single doses up to 200 r has therapeutic possibilities. The tolerated dose is beyond that necessary or desirable for leukemia but is in the effective range for lymphosarcoma and multiple myeloma. The patient who received 200 r on two occasions in three weeks had a clinical response that could be described as impressive.

No agent currently in use for treatment of generalized cancer is offered with intent to cure. Even increased survival as a result of therapy is difficult to confirm. Under these circumstances the principal benefit of treatment is early relief of signs and symptoms and this benefit may be mitigated by the severity of side effects of treatment, prolongation of treatment or delayed response to treatment. In all these respects, the administration of single doses of total body irradiation has some advantage.

There is an additional advantage in the matter of dose. Prescription of radiation dose is unique in its precision. It is possible under controlled conditions to deliver a desired amount to any tissue or to calcu-

late what has been delivered to any site. To relate dose and effect, it is desirable to determine dose at the site where effect is produced, so that a given result can be repeated or modified. Prescription of dose of pharmaceutical agents is usually on the basis of body weight, administered intravenously, orally, or intramuscularly. In the processes of absorption, dilution and transportation, the amount of the agent finally producing an intracellular chemical effect must be subject to wide and unpredictable variations. If the clinically effective dose closely approaches the tolerance dose, it is desirable to have knowledge and control of the amount of concentration of an agent at the cellular level where its effect is exerted.

SUMMARY

Total body irradiation in a single exposure up to 200 roentgens of 250 kilovolt roentgen rays may be safely administered to patients with generalized cancer. Considered as one form of systemic therapy rather than as an alternative or competitive method of treatment, total body irradiation in doses of this order is a useful addition to the management of advanced cancer.

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RADIUM INHALATION ACCIDENT—RADIUM EXCRETION STUDY

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MUCH of our present knowledge about the clinical effects of heavy radio-elements has been obtained from the industrial and internal therapeutic use of radium. Information gained from the clinical effects of radium has been the foundation upon which the permissible levels of exposure for other radio-elements have been built.

Relatively few data are available on the excretion of radium after inhalation, ingestion or internal administration in humans. Additional information is also needed as to the most sensitive and adequate means for evaluation of exposed individuals.

Several accidents have occurred in recent years in which 10–100 mg. sources of radium were broken, exposing personnel to inhalation or ingestion of the contents. Since 10 mg. of radium is many times the severely damaging dose the management of exposed personnel is of medical importance. Precautionary measures to prevent and to minimize such accidents have been outlined by Saenger, *et al.*[37] This is a report of one of those accidents, information obtained from it, and discussion relating it to incidents of a similar nature.

ACCOUNT OF ACCIDENT

On August 1, 1952, two men were calibrating radiation dosimeters using a 50 millicurie encapsulated mixture of radium and barium sulfate. The radium capsule was fitted into a small lucite cylinder in a device which used compressed air to raise the capsule to the calibrating position. On this day, the radium capsule did not rise to position in response to the air pressure. Without turning off the air, patient A.N. inserted a lucite wand into the pneumatic tube. This dislodged the capsule and the compressed air pushed it into the calibrating position. It was noted immediately that the lucite cylinder containing the radium was broken and some fine powder was visible. The compressed air and wall fans were turned off, and a window was opened. The damaged lucite cylinder and the radium source were placed in a paper cup and lowered into a lead brick enclosure. The existence of a radium spill was promptly confirmed with a survey meter, the room was locked and the health physicist was notified. The windows were left open continuously until the room was reoccupied. Later measurements revealed that not more than 3 mg. of radium escaped from the capsule.

A survey meter gave no evidence of contamination of patient H.C., but gave readings of 0.3 mr to 5 mr/hr. on the clothes, fingers, and face of patient A.N. Patient A.N. then washed his hands twelve times with detergents and citric acid, and took six showers using detergents and citric acid. His mustache was shaved off and shown to be contaminated. Nasal secretions from both patients showed contamination when counted with an end window Geiger-Müller counter. The nasal passages of patient A.N. were swabbed once with a neosynephrine solution, to lessen absorption from the mucous membranes, and then swabbed and washed three times with a normal saline solution.

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Part of the information in this paper was incorporated in a Report (8/P/479) "A Summary of Radium and Thorium Excretion in Humans" by Looney, W. B., Hursh, J. B., Archer, V. E., Steadman, L. T., and Colodzin, M., for the First International Congress on the Peacetime Uses of Atomic Energy, Geneva, Aug. 8–20, 1955.

The opinions and assertions contained herein are the private ones of the author and are not to be construed as official or reflecting the view of the Navy Department or the Naval Service at large.

Table I

BLOOD STUDIES

Patient	Date	Red Blood Cells	White Blood Cells	Hemoglobin	Polymorphonuclear Leukocytes	Lymphocytes	Monocytes	Eosinophiles	Band Cells
A.N.	8-1-52	4,600	13,100	14	72	26		2	
	8-2-52	5,000	9,650	14.5	69	29	1	1	
	8-3-52	5,000	8,850	14.0	74	22	1	3	
	8-4-52	5,300	9,450	14.5	66	30	1		
	6-8-53	5,400	7,700	14.5	61	31	3	2	3
H.C.	8-1-52	5,000	10,000	15	68	30	0	0	2
	6-8-53	5,150	6,800	14.5	60	34	0	0	6

On August 2, the room in which the accident occurred was surveyed and found to be heavily contaminated. At this time an air dust sample was collected with a hand operated filter paper sampler. This showed 1.6 $\times 10^{-12}$ curies per liter of gross activity. This activity was most probably radon and its daughter products as it decayed rapidly. As the collection was poorly controlled, this figure is not quantitative, but indicates that the concentration was greater than the normal air concentration for radon. On August 15, a quantitative determination of radon in the air of the room showed a concentration of 13.6×10^{-12} curies per liter. After weeks of thorough decontamination of every exposed surface in the room, the room was reoccupied. On September 26, the radon content of the room air was 0.28×10^{-12} curies per liter which is only a little above the normal content of room air in this vicinity.

STUDY OF PATIENTS

The patients were admitted to the United States Naval Hospital, Bethesda, Maryland on August 1. Physical examination on admission was negative. At no time did either of the patients have any symptoms which might be attributed to the inhalation of radon or radium.

The anterior and posterior surfaces of the chest were marked off in areas approximately 10 cm.^{2} and a chest survey made with a lead collimated Geiger-Müller counter in both patients. In the region of the main bronchi counts slightly above background were detected for four days in patient A.N. The fact that these increased counts occurred only in this area is suggestive that radium was deposited. However, this cannot be considered significant because the counts were within the statistical limits of background variation.

Chest roentgenograms of both patients, taken on August 1, 1952, showed no abnormalities.

Each patient had three consecutive blood studies on admission. The average of these three and the single determinations made on subsequent days are given in Table 1. The leukocyte counts of patient A.N. were elevated on the first day and returned to normal values on the second day. Patient H.C. had a questionable elevation of the leukocytes.

Breath samples for radon breath determinations were collected by having patients breathe at a normal rate, exhaling into a three-liter rubber bag. Collection was stopped before any pressure for actual expansion of the balloon was necessary. The rubber bag was connected to, and its contents immediately transferred to a one-liter glass flask which had been evacuated. Radon breath determinations* of samples taken seven hours after the accident were about five and two times greater than background respectively (see Table II). The

* Analyses were made by the Radioactivity Section of the National Bureau of Standards.

TABLE II

RADON BREATH MEASUREMENTS

Patient	Date	Radon[a] in $\mu\mu c/l$	Net Radon[b] in $\mu\mu c/l$	Estimate[c] X of Retained Radium	Estimate[d] Y of Retained Radium	Estimate[e] Z of Retained Radium
A.N.	8-1-52	0.77	0.60	34,200		7,800
	8-2-52	0.57	0.40	22,800		5,010
	8-3-52	0.25	0.08	4,560	6,460	3,460
	8-4-52	0.34	0.17	9,670	5,160	3,130
	8-5-52				3,870	2,870
	8-6-52	0.26	0.09	5,120	2,580	2,540
	8-7-52				1,290	2,490
	8-8-52	0.17	0.0	0.0	0.0	2,430
Control	8-6-52	0.17				
A.N.	6-8-53	0.10	0.0			520
H.C.	8-1-52	0.30	0.13	8,000		60
	6-8-53	0.10	0.0	0		

[a] Curies$\times 10^{-12}$ per liter of exhaled air.

[b] The control value of 0.17×10^{-12} curies/liter for room air was subtracted from the amount of radon in the exhaled air to give net radon.

[c] In $\mu\mu c$, direct calculation of retained radium assuming that the patient was breathing at the rate of 5 liters per minute and that the radon-radium ratio was 0.7.

[d] The average of the direct values for the third, fourth and sixth days was 6,460 $\mu\mu c$. This value was assigned to day 3 and on successive days one-fifth of this value (1,290 $\mu\mu c$) was subtracted to give the value for the following day.

[e] In $\mu\mu c$, the estimate of retained radium obtained from excretion data.

level of A.N. gradually dropped to background levels eight days after the accident. Radon breath determinations on both patients, one year following the accident were within normal limits.

Daily urine and fecal specimens were collected on patient A.N. the first week and only the first day on patient H.C. Excreta were collected on both patients at intervals thereafter. The urine and feces were analyzed separately by the method of Russell, Lesko and Schubert.[35] For maximum sensitivity and to eliminate sampling errors, the entire twenty-four hour specimens were analyzed. The dried samples were counted in a commercial gas flow proportional counter. By this method 5×10^{-13} grams of radium could be determined satisfactorily. The results of the analysis are given in the third and fourth columns of Table III. It will be noted that the amount of radium excreted in the urine of both patients rapidly fell to near background levels within the first week. The radium content in the feces of patient A.N. has been significantly elevated for more than one year.

DISCUSSION

A. Excretion Data. In Figure 1, a curve is drawn from the semi-log plot of total daily excretion from patient A.N. The excretion data of Aub, *et al.*[1] Seil, Viol, and Gordon,[46] Rajewsky and Muth[32] and Marinelli, *et al.*[24] are also plotted (with values divided by the indicated factor so that they would fall in the same area) on the same graph. With the exception of patient X of Rajewsky and Muth[32] who had early therapy, the excretion curves are nearly identical, even though the route of radium intake differed. In the characteristic curve there is a rapidly decreasing amount of radium excreted per day for the first five to eight days after intake, followed by a prolonged period of slowly decreasing excretion per day. The failure of the excretion curves of 2 of the cases of Seil, Viol, and Gordon[46] and case B of Rajewsky and Muth[32] to show the sharp break at five to eight days may be due either to too short a period of study or to a lack of sensitivity of the method of analysis. If the value at six months for the patient of Aub, *et al.*[1] was

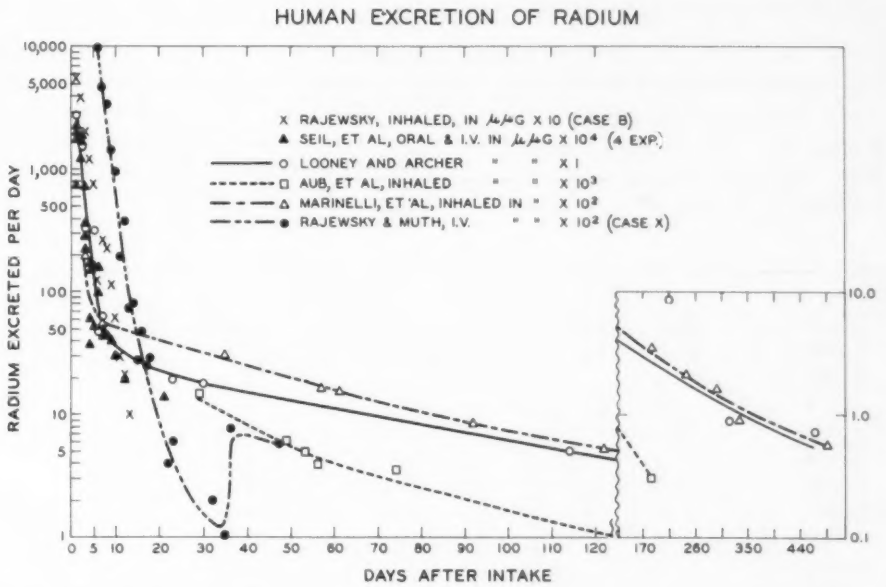
HUMAN EXCRETION OF RADIUM
RADIUM EXCRETED PER DAY
DAYS AFTER INTAKE
X RAJEWSKY, INHALED, IN μμG X 10 (CASE B)
▲ SEIL, ET AL, ORAL & I.V. IN μμG X 10⁴ (4 EXP.)
O LOONEY AND ARCHER " " X 1
□ AUB, ET AL, INHALED " " X 10³
△ MARINELLI, ET AL, INHALED IN " X 10²
● RAJEWSKY & MUTH, I.V. " " X 10² (CASE X)
10,000
5,000
1,000
500
100
50
10
5
1
10.0
1.0
0.1
0 5 10 20 30 40 50 60 70 80 90 100 110 120 170 260 350 440

FIG. 1. Radium excretion curves in humans. The four experiments of Seil, Viol and Gordon (two orally and two intravenously administered) have been designated by the same symbol. Case x of Rajewsky and Muth represents urine excretion only while all the other curves represent the total of urine and feces. Aub and Evans questioned the accuracy of the last point for their patient.

low as they suggested then his curve would be more nearly parallel to the others. It seems from Figure 1 that a period of rapid elimination of radium occurs within the first week regardless of the route of entry.

In his review article on the mechanism of removal of foreign material from the lungs, Robertson[34] concluded that material that had not penetrated beyond the terminal bronchi was rapidly swept out by ciliary action while material in the alveoli was removed by macrophages. Scott, *et al.*,[45] concluded from their experiments on rats that the principal route of elimination of uranium, plutonium, and protoactinium particles (in either soluble or insoluble forms having an average diameter of 0.5 to 1 micron in diameter) was mechanical removal via the trachea with subsequent swallowing, since relatively little activity was demonstrated in the lymphatics and blood vessels of the lungs of the animals. He also showed that particles of these different elements were removed from the lungs at comparable rates despite their different chemical and physical natures. Schubert[44] states that the precipitation pH of an element is the principal factor governing passage of that element from the lungs into the blood stream. If he is correct, then thorium, plutonium, uranium, protoactinium and radium should all form insoluble compounds when deposited in the lung even if they were in a soluble form on entrance.

If we assume that the mechanism of removal of plutonium and uranium from the lungs of man is similar to the mechanism in rats, if we assume that plutonium, uranium, and radium all automatically form insoluble compounds in the lungs, and if we assume comparable particle size, then we would expect that the rate of elimination of inhaled plutonium and uranium by Scott's rats would be similar to the rate of elimination of inhaled radium in our patients and in those studied by Marinelli, *et al.*[24] These data indicate that a similarity exists between the rates of elimination of these radio-elements in the reported human cases and in animals.

Of the radium that he was estimated to have received, based on excretion measurements, patient A.N. eliminated 50 per cent

TABLE III

ELIMINATION DATA

Day	Radium in Body μμg* (estimated)	Radium Excreted in μμg.			Daily Elimination		
		Urine	Feces	Total	Per cent of retained radium	Per cent of original dose	Per cent of daily elimination via feces
Patient A.N.							
1	7,800	87.8	2,702	2,789.8	35.9	35.9	96.8
2	5,010	28.4	1,520	1,548.4	30.9	19.8	98.2
3	3,460	14.9	314	328.9	9.5	4.2	95.5
4	3,130						
5	2,870	1.9	323.6	325.5	11.3	4.2	99.4
6	2,540	2.3	45.0	47.3	1.9	0.61	95.1
7	2,490	0.2	61.5	61.7	2.5	0.79	99.7
23	1,990	0.8	18.9	19.7	0.98	0.25	95.9
30	1,870	0.7	17.6	18.3	0.97	0.23	96.2
114	1,054		4.9		0.46	0.063	
217	660		8.8		1.33	0.11	
315	510		0.9		0.18	0.01	
465 and 466	360		1.45/ 2 days		0.20	0.009	
Patient H.C.							
1	60	7.2	14.8	22.0			
25		0.0	.9				
37			1.8				
45			2.5				

* The first value for body radium was obtained from calculations shown in the text. Subsequent values were obtained by subtracting the amount eliminated.

during the first two days, and 10 per cent during the next three days. About 97 per cent of this was eliminated in the feces, the rest in the urine (Table III). This agrees with all other human data following the intravenous administration, inhalation or ingestion of radium in which 90–99 per cent of the radium was eliminated in the feces.[47] The urine-feces ratio of patient A.N. did not change appreciably during the first four weeks he was followed. If the radium was removed from the lungs primarily by mechanical action and subsequently swallowed, then it seems that it was absorbed from one part of the gastrointestinal tract and excreted into the tract at another. Since there is evidence that radium is excreted in bile,[1,38] it suggests the possibility that radium is absorbed from the stomach or upper duodenum and then re-enters the gastrointestinal tract with the bile. If the swallowed radium was not absorbed and re-excreted into the intestinal tract, then it would seem that a change in the urine-feces ratio should have occurred following the elimination of the unabsorbed radium.

The changing coefficient of elimination (the amount eliminated per day divided by the body content) of radium for patient A.N. is graphed in Figure 2, along with others from the literature.[1,22,29,30,31,39,40,41,46] It corresponds closely with that calculated for the patients of Marinelli, *et al.*[24] both of which are corroborated at various points by other reported cases.[1,41,46] Although 3 of the other cases were from inhalation similar to ours, it should be noted that the others received their radium intravenously

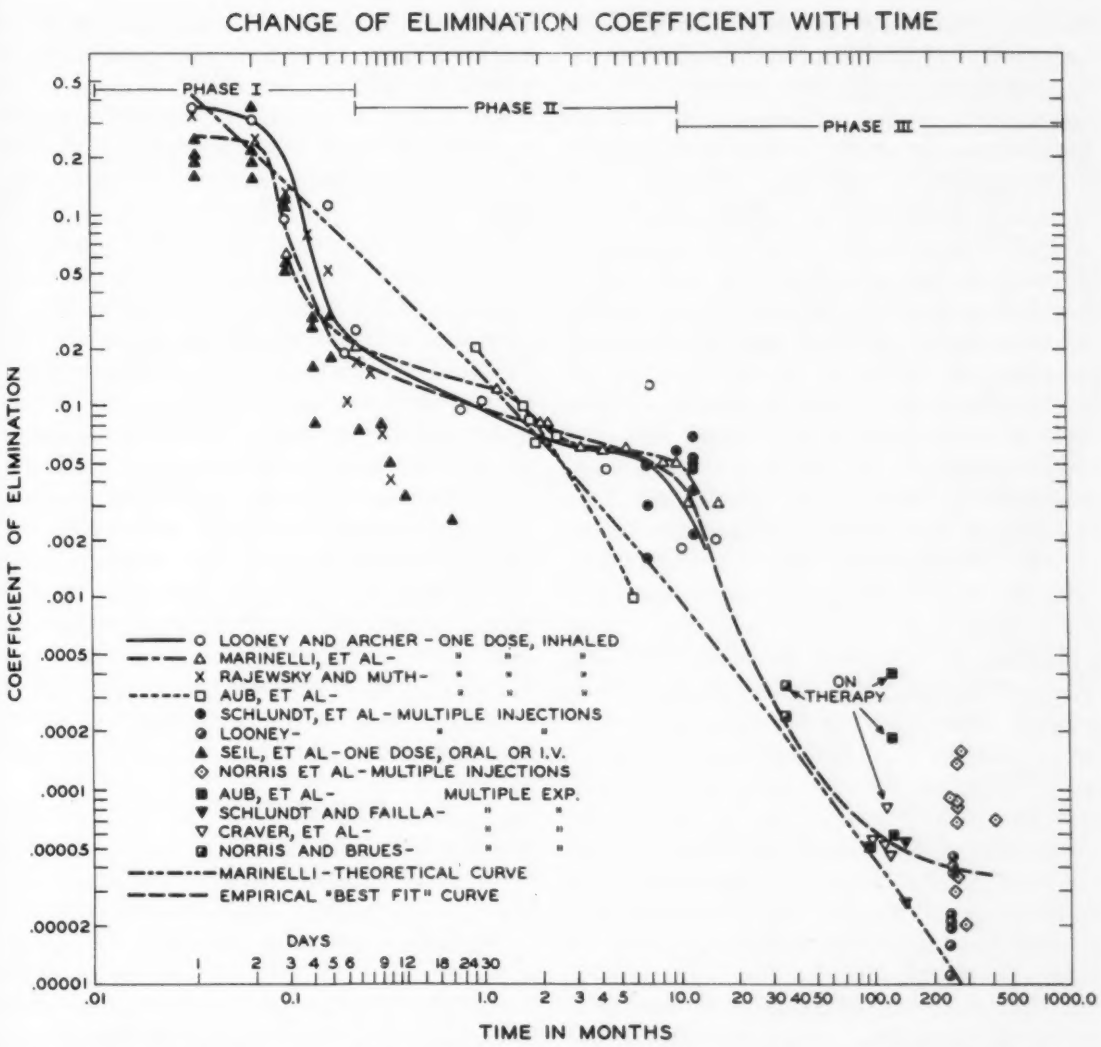

FIG. 2. Change of elimination coefficient of radium with time. The four experiments of Seil, Viol and Gordon (two orally and two intravenously administered) are designated by the same symbol. The patients reported by Schlundt, Nerancy and Morris at 7–12 months are largely the same ones reported by Looney at 240 months, and by Norris *et al.* at 240 to 420 months.

or orally. The only serious disagreements are those points near the termination of study of the cases of Seil, *et al.*,[46] of Rajewsky and Muth,[32] and of Aub, *et al.*[1] Since these points are derived from values near the minimum amount of radium measurable by the methods used, it is possible that they may have been low. The route of entry or the chemical and physical forms of radium may also have been contributing factors.

The coefficient of elimination curve may be divided into three phases. Phase 1 corresponds to the rapid elimination of the first week. It may represent radium eliminated from the soft tissues and blood stream. In case of ingestion it may also be due to elimination of unabsorbed radium from the gastrointestinal tract. Our data indicate that elimination in this way may be less important than was formerly considered.

Following Phase 1 there is a gradual decrease in the coefficient of elimination of

radium for nearly a year. The data of Cameron and Viol[5] and of Van de Putte[50] suggest that considerable amounts of radium remain in the organs and soft tissue for months in man. These investigators reported the liver had higher concentrations of radium than bone at one month and at two to three months the concentrations in the liver, spleen and lung were not greatly lower than in bone. This is in contrast to the distribution in the long standing cases in which 95–99 per cent of the radium is in the skeleton.[12] However, more precise data in dogs showed less than 2 per cent of the remaining radium in the soft tissues only a few days after administration.[30] This is Phase II and it probably represents the elimination of radium from the more accessible parts of the skeleton and possibly from soft tissues.

During Phase III there is a continuing gradual decrease of the coefficient of elimination from about 0.005 at one year to about 0.0003 at twenty years. This probably represents the removal of radium from the less and less accessible parts of the skeleton until eventually it is the result of the removal of radium from destroyed areas of bone. The term, "fixed radium," has been applied to that portion of radium remaining after about one year. It should be pointed out that in a study of a group of mental patients given radium (1930), one-half of the estimated retained radium at one year was eliminated during the subsequent nineteen years.[22] It is evident that this would be of considerable significance in the management of cases in which young individuals receive maximum or near maximum permissible amounts of bone seeking radioelements. It might mean the difference between continuing one's work with radioactive materials or stopping it.

B. Hematological Data. The leukocyte count of patient A.N. was mildly elevated and that of patient H.C. was questionably elevated on the day of exposure and at normal levels thereafter (Table 1). The reason for this rise is not clear but it may have been due to emotional stress, to inhaled radium or to inhaled radon. Although it seems unlikely that the leukocytosis was a radiation effect, an elevated leukocyte count was noted in several exposed individuals on the day following a previous radium accident involving inhalation of material from a ruptured radium capsule.[36] In the period around 1915 when radon was used in the treatment of a large number of diseases, there were several articles which reported a leukocytosis following the inhalation or ingestion of radon.[26] Inama[19] reported an increase in both the leukocyte and erythrocyte counts following exposure to radon in Austrian caverns.

C. Previous Exposure to Ionizing Radiation. Neither of our patients had any known internal exposure to radio-elements prior to the accident. As recorded on personnel film dosimeters, the external radiation exposure of patient A.N. was 11.1 rem since his employment in February of 1950; that of patient H.C. was 10.2 rem since his employment in February of 1951.

ESTIMATION OF RADIUM RETAINED BY THE BODY

A. From Excreta. By use of excretory data, there are three ways of estimating the body radium when the amount of intake is not known. One is to divide the amount excreted in a given day by the coefficient of excretion for that day if it is known. Theoretical curves have been proposed by Hoecker,[18] Marinelli, *et al.*,[24] and by Norris *et al.*[30] to determine this coefficient. These curves are compared with our "best fit" curve that has been drawn to cover the period from one day to twenty years. The second method is to apply the formula of Cowan, *et al.*[7] The third method is to make a prolonged study of the amount excreted. The summation of the amount eliminated gives an estimate of the total amount of radium ingested or inhaled.

By use of the third method we have been able to make a rough check on the first two methods. By integrating the excretion curve we find that in 466 days, patient A.N. has excreted approximately 7,440 μμg. of

radium. We added 360 μμg. (our estimate of retained radium at 466 days) to this value to give us an estimate of 7,800 μμg. as the original intake. The value of 360 μμg. for retained radium at 466 days was arbitrarily chosen on the basis of other reports that at one year after intake of radium about 1 to 10 per cent remains[2] in the body with an average of 2 to 5 per cent after inhalation.[31] Our figure is 4.6 per cent of 7,800.

The inherent difficulty with estimates based on excretion measurements is the individual variation of the coefficient of elimination. Norris, *et al.*[30] found that the coefficient of elimination varied from .002 to .016 in patients who had radium present in their bodies for over twenty years. It would be expected that the variation would be greater shortly after ingestion or administration when the rate of elimination is changing much more rapidly.

We were unable to make similar calculations for patient H.C. because of the meager excretory data. However, for rough calculations, if we assume that he excreted 36 per cent of the inhaled and ingested radium in the first day (as did patient A.N.), then he may have had an intake of 60 μμg. Since patient H.C. re-entered the contaminated area, calculations based on the excretions of the twenty-fifth to forty-fifth days would be less valid.

The above values of 0.0078 μg. and 0.00006 μg. for amounts inhaled and ingested by patients A.N. and H.C., respectively, are much less than 0.1 μg. which is the maximum permissible amount for retained radium.[27]

B. From Radon Breath Determinations and Scintillation Counters. In evaluating the radon breath determinations three factors should be taken into consideration: (1) the room air twenty-four hours after the accident had a greatly elevated radon content, (2) the radium was in the form of radium sulfate co-precipitated with barium sulfate, and (3) errors of 100 per cent or more in radon breath determinations can occur because of the inherent difficulties in sampling.[48]

Two weeks after the accident the room air contained about seventy times the normal air radon levels even with the room open to the outside atmosphere. Elevated radon breath values would naturally occur as a result of breathing radon. Harley, *et al.*[7] found that people breathing radon took 1½ days to eliminate 95 per cent of the gas.

The radium was in the form of radium sulfate co-precipitated with barium sulfate. In this form nearly all of the radon is retained in the precipitate.[14,46] Even when the radium sulfate is finely divided, less than 5 per cent of the radon escapes.[46] When radium sulfate is taken into the gastrointestinal tract or lungs, how quickly is it transferred from the nonemanatory state to the emanatory state?

The amount of radium ingested or inhaled, as estimated by radon breath values on the first day is four and one-half times the values obtained by estimation from the excretion values. This discrepancy could be due to the elimination of the radon inhaled at the time of the accident.

Because of the fluctuation of values at days 3, 4, and 6 (Table II) they were averaged. If the body radium derived from this average (6,460 μμg.) is assigned to the third day and one-fifth of this value is subtracted for each day up until the eighth day when background is reached, then the values for the retained radium estimated by radon breath and excretion values are in fair agreement. Had a sample of radon of room air been taken at the time of the accident a reasonably good estimate of the quantity of radon inhaled might have been made. This would have permitted a more critical evaluation of the estimation of retained radium by excretion data compared to radon breath.

In view of the limitations mentioned, radon breath determinations do not seem to be the best means for estimating body radium shortly after an acute exposure. If facilities are available, however, they are an easy and rapid means for obtaining some estimate of the order of magnitude of the exposure.

Estimation of retained radium by external counting is probably more satisfactory than radon breath determinations. However, the same difficulty is encountered during the first two days since one is unable to differentiate the gamma rays of the daughter products of the inhaled radon from the gamma rays originating from the daughter products of the inhaled or ingested radium. Since the radon-radium ratio may be changing rapidly following radium ingestion or inhalation, one must rely on the summation of the estimates of retained radium by radon breath measurements and by external gamma ray counting.

It is known that radon breath determinations may vary more than 100 per cent even in patients who have retained radium for long periods of time.[10,25,32] This is caused by the inability to standardize the physiologic state and rate of exhalation of the patient, and by fluctuations in the radon content of the environment.

From the control values for the radon breath samples it can be seen that this method cannot accurately determine less than 0.2 micro-microcuries of radon per liter which is equivalent to a body radium content of about 0.02 μg. of radium. The lower limits of measurement with current scintillation counter techniques is between 0.05 and 0.1 μg. of retained radium. Technical developments in scintillation counters may eventually permit the estimation of much lower values.[4,33] These measurable limits of .02 to .1 μg. of retained radium may be compared to the limit of detectable radium in feces which corresponds to about 2 μμg.* in the body on the first day after intake and to 0.01 μg. of retained radium ten years after intake.

NOTES ON THERAPY

As it was evident soon after the accidental exposure that neither of our patients had inhaled or ingested an amount of radium which would approach the maximum permissible amount, no therapy was attempted. If early tests indicate an intake of hazardous amounts, early therapy would probably reduce bone deposition. Early therapy is emphasized because attempts at removal of radium from the body after a period of weeks or months have met with little success.[1,29]

The only case on record which received early therapy was Case x of Rajewsky and Muth.[32] He was given copious amounts of water, carbonates and ferric hydroxide orally. This treatment appeared to have some success because the period of initial rapid excretion (Fig. 1) lasted for approximately twenty days instead of the five to eight days shown by all other patients who have been studied.

The use of magnesium sulfate initially as a gastric lavage and then for daily purging has been advocated.[28,37]

The administration of parathyroid hormone, ammonium chloride and activated ergosterol[1,29] of citric acid and citrates[8,20,21,42] and of salts of ethylenediaminetetraacetic acid[6,12,13,15,23] have shown accelerated excretion of radium or of elements chemically similar to radium in animals or man. They should be considered for use in early therapy.

SUMMARY

A report is made of 2 cases of accidental radium inhalation. The excretion of radium by one was followed for over a year. Radon breath samples were considered to give a poor index of exposure in these cases. The efficacy of different methods of determining the body radium content is reviewed. The amount of radium inhaled was estimated from excretion data. It was found that 76 per cent of the inhaled radium was excreted in the first five days. The feces contained 97 per cent of the eliminated radium. These excretion data were added to data from the literature to illustrate the exponential decrease of the coefficient of excretion. Suggestions for therapy are made.

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* Values for radium excretion in unexposed individuals should be taken into consideration at these extremely low levels.

The authors would like to express their appreciation to Rear Admiral B. W. Hogan, Commanding Officer, Capt. E. F. Evans, Head of Medicine, Cdr. M. W. Mason, Head of Radiology and Cdr. E. R. King of the Radioisotope Laboratory, of the U. S. Naval Hospital, Bethesda, Maryland; to Dr. L. S. Taylor, Chief of Atomic and Radiation Physics, Dr. W. B. Mann, Head of Radioactivity Section and Mr. L. L. Stockman of the Radon Testing Section of the National Bureau of Standards; to Capt. W. M. Belts, Director of the Naval Research Laboratory and Dr. F. W. Westneat, Medical Officer of the Naval Research Laboratory for their cooperation and assistance in this study.

The technical assistance of Mrs. Isabelle B. Ackermann is gratefully acknowledged.

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Vol. 75, No. 3

LATE SKELETAL ROENTGENOGRAPHIC, HISTOPATHOLOGICAL, AUTORADIOGRAPHIC AND RADIOCHEMICAL FINDINGS FOLLOWING RADIUM DEPOSITION*

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INTRODUCTION

THERE have been previous studies made of skeletal roentgenographic changes in individuals who received radium medically or who had been employed as luminous dial workers.[1,2,6,8,11,12] Histopathologic studies from luminous dial workers and individuals who received radium medically were made recently. These specimens were obtained from 11 persons who had had radio-elements deposited in their bodies for periods ranging from twelve to thirty-five years. Animals given bone-seeking radio-elements, such as radium, strontium, plutonium, and yttrium, exhibited skeletal histopathologic changes similar to those seen in man.[3,4,7] Since the roentgenographic changes in the radium patients and luminous dial workers are the result of the histopathologic changes, it is reasonable to assume that similar roentgenographic changes would occur in man following the inhalation or ingestion of such radio-elements as plutonium and strontium. These minor skeletal roentgenographic changes may eventually be one of the more reliable clinical means for the early detection of radio-elements whose primary sites of deposition are the skeleton.

SOURCE OF MATERIAL AND TECHNIQUES

It has been possible to demonstrate by autoradiographic studies the manner of deposition of radium in the skeleton; by histologic studies, the histopathologic changes that have taken place; and by roentgenographic studies, changes that have occurred as a result of the histopathologic changes. The material for this study was obtained at autopsy from a patient who died in 1951 from an osteogenic sarcoma of the foot (age forty-eight years). She had received radium water orally for "migrating polyarthritis" (at the age of twenty-six years). Several sections of the femur, humerus, tibia, fibula, and skull were made in order to have representative gross autoradiographs of the osseous skeleton. Roentgenograms of each of the serial sections were also made. The gross autoradiographs and roentgenograms were used as a guide for selections of specimens for histopathologic, detailed autoradiographic, and radiochemical studies. The detailed autoradiographs and histopathologic specimens were selected from areas which it appeared would yield the most information on the relation of radium deposition and skeletal change.

OBSERVATIONS

(A) *Roentgenographic, Autoradiographic and Histopathologic Findings.* Radium was found to be irregularly distributed throughout the cancellous and compact bone (Fig. 1). In compact bone only a small percentage (10–15 per cent) of the haversian systems and interstitial lamellae had appreciable concentrations of radium. In some instances it was deposited in one or two concentric lamellae (Fig. 2 and 3). In other instances it was deposited around the central canal or the periphery of the haversian system, or distributed throughout the

* Presented (in part) at the Fifth Inter American Congress of Radiology, Washington, D. C. April 24–29, 1955.

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FIG. 1. This is an autoradiograph of an entire section of tibia demonstrating the irregularity of distribution of radium in bone. The small areas of concentration seen in the proximal end extend down into the shaft as far as the cancellous bone extends. In the distal end the concentrations are near the articular surface. Note the linear area of concentration adjacent to the articular cartilage which outlines the ends of the shaft. The areas of radium concentration in the shaft are not numerous. Observe the diffuse less dense outline of the shafts. (Courtesy A.M.A. Arch. Path., 1953, *56*, 1–12.)

haversian system (Fig. 4).

Areas of radium concentration in cancellous bone were usually 5 to 15 microns in the greatest dimensions. However, there was a wide range in size of these areas (Fig. 5). In some instances linear concentrations ran parallel to the curvature of the trabeculae for 50 to 100 microns (Fig. 6). Heavy and rather uniform concentrations of radium were present at the junction of the articular cartilage and the trabeculae (subchondral plate). These frequent, small, highly-concentrated areas outlined the bone contours of the ends of some bones (Fig. 1 and 7). Cementing lines were clearly outlined by heavy radium concentrations in some instances.

Atypical osseous tissue was found adjacent to the trabeculae in some areas (Fig. 5, 8, 9, and 10). Destruction of the trabeculae was found in some areas, hypertrophy occurred in others (Fig. 8 and 9). Acellular fibrous connective tissue was found throughout the trabecular spaces (Fig. 8, 9, and 10). The atypical osseous tissue was demonstrated roentgenographically as small areas of increased density (Fig. 11).

Well defined areas of destruction which usually were replaced with fibrous connective tissue were found in compact bone. Some central canals showed a wide variation in size. In some instances the entire haversian system was almost completely destroyed. Other central canals were occluded with a dark-staining material, similar to the atypical osseous tissue found in the trabecular spaces (Fig. 12, 13, and 14). Some haversian systems appeared to have undergone periods of resorption from the central canals followed by periods of redeposition of bone (Fig. 13). Usually there was minimal evidence of bone regeneration. Macroscopic areas of destruction which were about 1 to 2 mm. in width and 5 to 20 mm. in length (Fig. 14) were also absorbed. These areas of bone necrosis resulted in small areas of decreased density found on skeletal roentgenographic examination (Fig. 15). The roentgenogram of the humerus is shown in Figure 16. The characteristic skeleton roentgenographic pattern seen in these patients is demonstrated in this roentgenogram, namely, areas

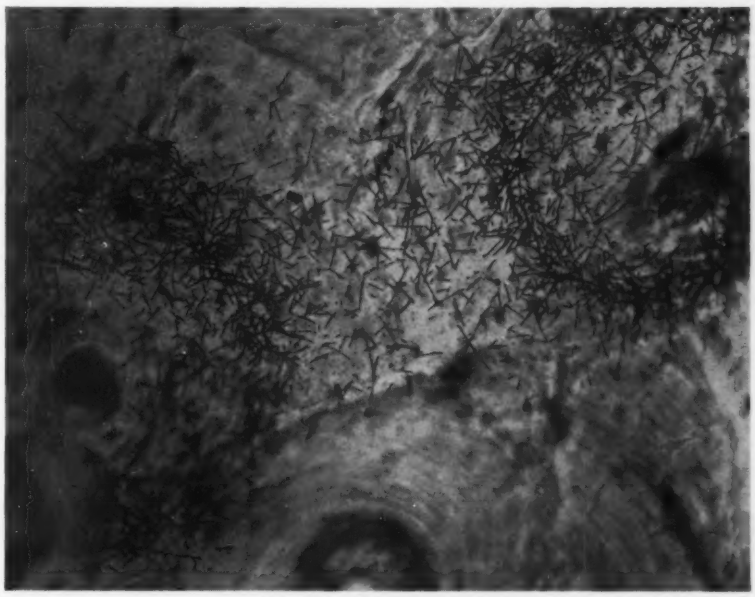

Fig. 2. This is a photomicrograph of a detailed autoradiograph of an undecalcified section of compact bone showing alpha tracks coming from two haversian systems. Note that the remainder of the field is relatively free of activity. Only about 10–15 per cent of the haversian systems had high concentrations of radium. The infrequent occurrence of small highly concentrated areas of radium in compact bone was also demonstrated in the gross autoradiograph of the shaft of the tibia (Fig. 1). (Courtesy A.M.A. Arch. Path., 1953, *56*, 1–12.)

of increased density in cancellous bone and areas of decreased density in compact bone.

Roentgenograms of three serial sections of the fibula demonstrate these areas of destruction in the middle of the cortex (Fig. 17). Gross autoradiographs were made of these serial bone sections (Fig. 18). The radium is concentrated in small deposits near the periosteum. Few of the areas of bone destruction coincided with the areas of radium concentration when the roentgenogram and the gross autoradiograph of a bone section were superimposed. Radium concentrations were rarely found around these macroscopic areas of necrosis. Bone destruction was found as often in the absence as in the presence of radium concentrations in the haversian systems (Fig. 3).

(B) *Malignant Changes.* The malignant tumor of the skeleton which developed in the tarsal scaphoid was first diagnosed as

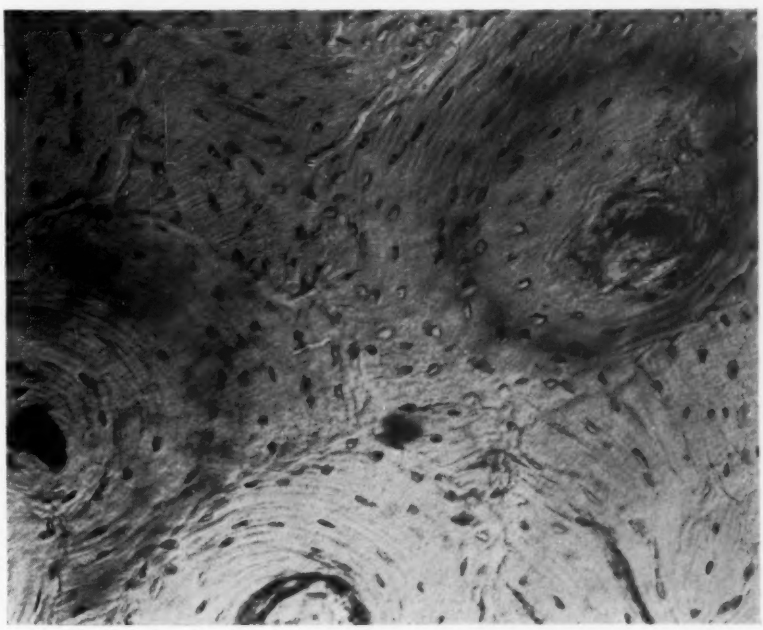

Fig. 3. This is a photomicrograph showing the underlying bone (Fig. 2). Note the darkening rings, showing that the radium was concentrated primarily in two concentric lamellae. One of the haversian systems is undergoing destructive changes and the other one is relatively normal. (Courtesy A.M.A. Arch Path., 1953, *56*, 1–12.)

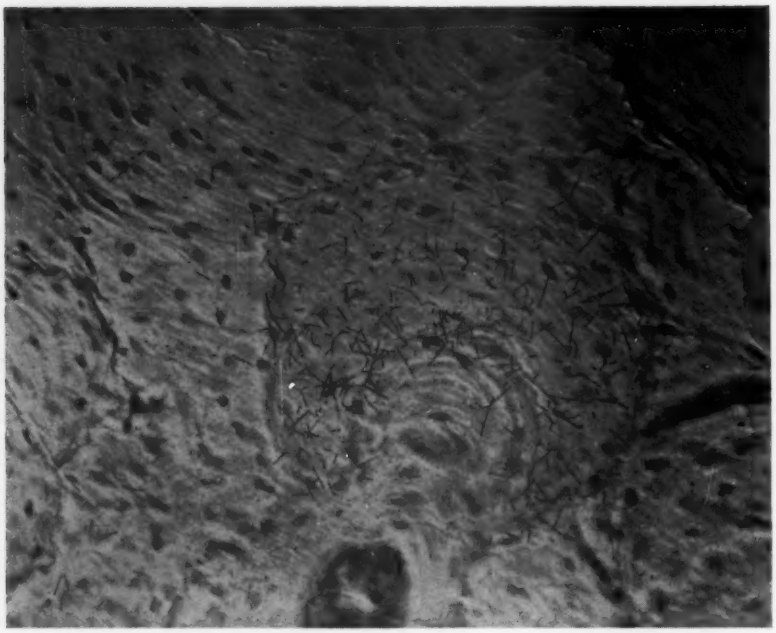

FIG. 4. This is a photomicrograph of an autoradiograph of an undecalcified section of compact bone. The alpha tracks are rather evenly distributed throughout the haversian system in the center of the photomicrograph and there is almost no activity in the remainder of the field. There are practically no alpha tracks in the new bone which has replaced the lower part of the haversian system.

FIG. 5. This is a detailed autoradiograph of cancellous bone. Note the irregularity of distribution of alpha tracks throughout the trabeculae and the atypical osseus tissue on each side.

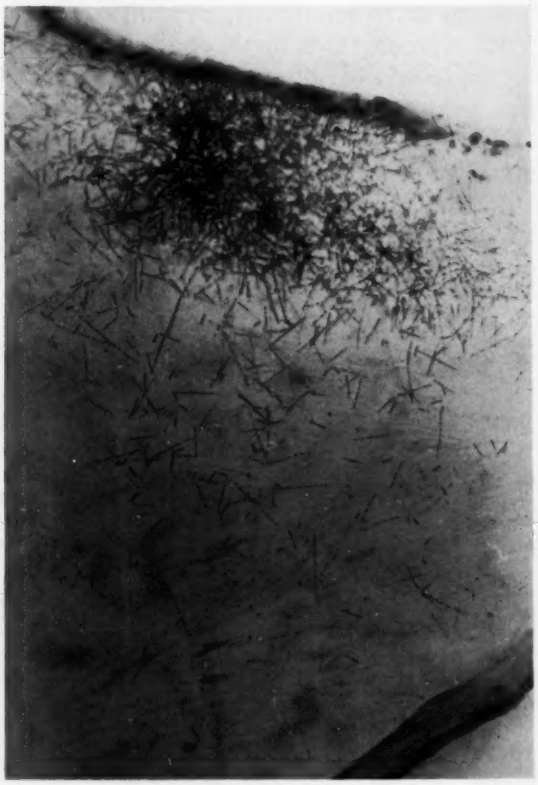

FIG. 6. This is the base of a large trabecula. Note the heavily concentrated area. The linear concentration beginning at the top of this area extended for a distance of 50–60 microns parallel to the curvature of the trabecula. (Courtesy A.M.A. Arch. Path., 1953, *56*, 1–12.)

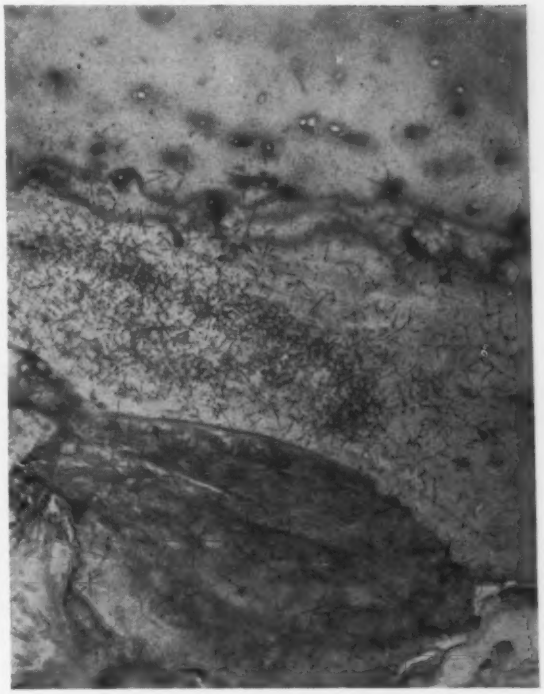

Fig. 7. This is a photomicrograph of an autoradiograph of the junction between the articular cartilage (subchondral plate) and cancellous bone of the head of the humerus. The articular cartilage is at the superior surface with almost no alpha tracks present. Just beneath the articular cartilage is bone with heavy concentrations of alpha tracks. Relatively few alpha tracks are in the atypical osseous tissue at the lower part of the photomicrograph. This linear concentration of radium at the junction of the articular cartilage and cancellous bone outlined the ends of the long bones (Fig. 1).

aseptic necrosis in 1947, six months after the onset of pain in the left foot (Fig. 19). A histologic section taken from a biopsy in 1950 showed the bone being destroyed by the fibrosarcoma (Fig. 20). A histologic section taken from one of the tarsal bones, following amputation of the leg in 1951, is shown in Figure 21. Complete destruction of the tarsal scaphoid and marked destruction of the other bones of the foot were demonstrated by roentgenographic examination in 1951 (Fig. 22). The finding of widespread metastases throughout the skeleton at autopsy suggests that malignant changes had occurred at multiple sites (Fig. 8).

(C) *Radiochemical Analyses.* Numerous radiochemical analyses were made of different bones and different parts of the same bones in an attempt to determine the variation in radium concentration in the skeleton.[13] The concentrations in specimens from the humeral head were 5.6, 1.1, and 2.6 $\times 10^{-10}$ curies per gram of ashed bone (Fig. 11). Specimen 5-C-2 was taken from

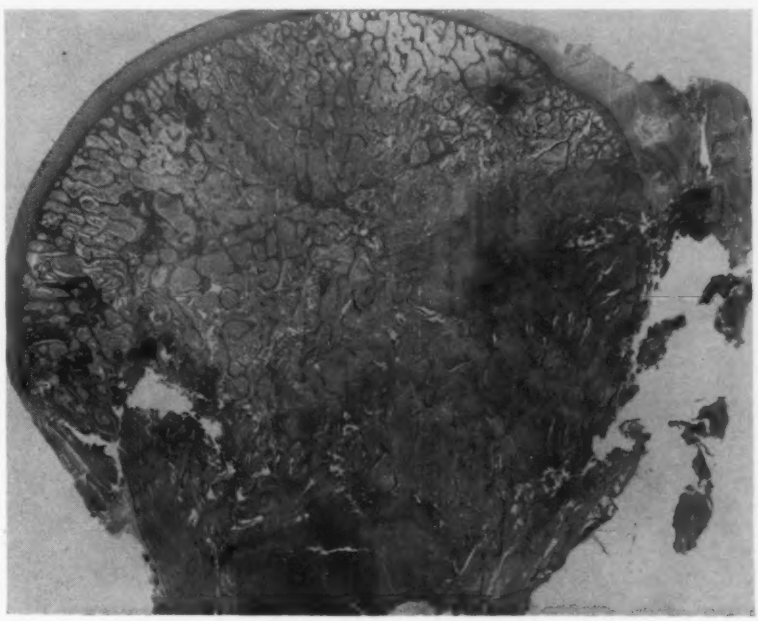

Fig. 8. This is a photograph of a histological section of the entire head of the humerus. Note the dark staining atypical osseous tissue near the articular surface on the left. The cancellous bone of the head on the right has been replaced with connective tissue and the fibrosarcoma.

FIG. 9. This is a magnification of one of the areas near the articular cartilage showing the atypical osseous tissue deposited in the trabecular spaces. Note the acellular fibrous tissue filling the remainder of the trabecular spaces. (The articular cartilage is shown on the right.)

a section of the humerus in which a large area of radium concentration was demonstrated on the surface by gross autoradiography. The specimen had less radium per gram of ashed bone than any of the other specimens analyzed. Samples were also taken from the bones of the foot and from the tumor area when the leg was amputated in 1951. The concentrations of radium in the 16 specimens taken from different parts of the skeleton varied by a factor of 11 (1.1×10^{-10} to 12×10^{-10} curies of radium per gram of ashed bone).*

Radium is considered to be similar to lead in distribution and mode of excretion.[6]

* Estimation of total body radium by external measurements was 1.3 micrograms. Estimation by taking the average radium concentration of the 16 specimens was 0.75 micrograms.[9,13]

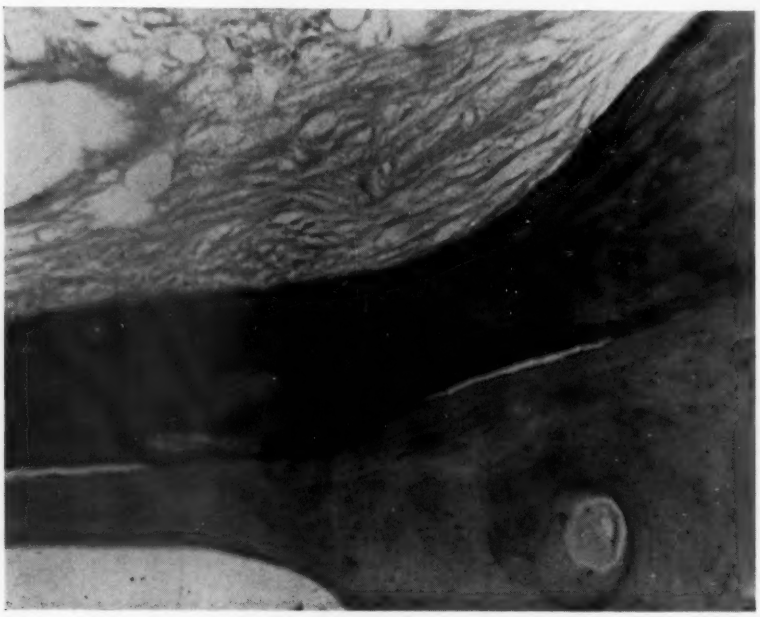

FIG. 10. This is a magnification of Figure 8 and 9 showing the cancellous bone, the darker atypical osseous tissue and acellular fibrous tissue.

Ninety to 99 per cent is rapidly eliminated and almost all of the retained radium is irregularly deposited in the skeleton.[2,8,10,12,13,15]

Some investigators have thought that the radium is redistributed throughout the skeleton whereas others believe this to be an apparent redistribution as a result of selective excretion from the more accessible parts of the skeleton.[1,5] Results from these investigations would seem to indicate that radium is eliminated more readily from the parts of the skeleton with the greatest surface area and from the bone with a better vascular supply. The linear concentrations outlining the ends of the long bones with one surface opposed to cartilage would have a small surface for exchange with body fluids. Although some redistribution probably occurs, it would seem from the detailed autoradiographic studies that the major part of the radium remains at the original site of deposition at the time of administration or ingestion. The amount eliminated after one year is very small and the coefficient of elimination of radium at ten to twenty years is only about .002 to .016 per cent of the body content.[13,14,15] For example in Figure 4, part of an old haversian system has been destroyed and replaced by new bone with no activity present. The small elimination of radium after one year is probably the result of the partial or total destruction of the haversian systems which have these marked concentrations of radium.

The results of the radiochemical studies on this patient demonstrate the limitations of radiochemical analysis for the study of skeletal radio-element deposition. The radium was usually highly concentrated in volumes which could be measured in microns while the smallest specimens that can be satisfactorily obtained for radiochemical analysis are measured in centimeters or millimeters. The radiochemical as well as the autoradiographic studies emphasize the inherent difficulties and limitations that will be encountered in any attempt to calculate the ionizing irradiation delivered to bone from internally deposited radio-elements.

FIG. 11. This is a roentgenogram of a 2 mm. section of the humeral head. The area of increased density immediately beneath the lower boundary of the section 5-C-2 was the result of the presence of atypical osseous tissue. See Figure 8 and 9 and note the atypical osseous tissue at the same location. (Radium concentration expressed as curies per gram of dried bone.)

(D) *Relation between Radium Deposition and Pathologic Changes.* Reconstruction of the relation between radium deposition and pathologic changes of a process of twenty to thirty years' duration is difficult. Little radioactivity was found in the macroscopic areas of destruction demonstrated microscopically and roentgenographically. It has been considered that the radium was removed by the time the destruction occurred.[2] This probably does happen in some instances; however, in the extensive serial

FIG. 12. This is a longitudinal section of compact bone. Note the destroyed bone is replaced with fibrous connective tissue. The central canal in the center is occluded with a dark staining material similar to the atypical osseous tissue found in cancellous bone.

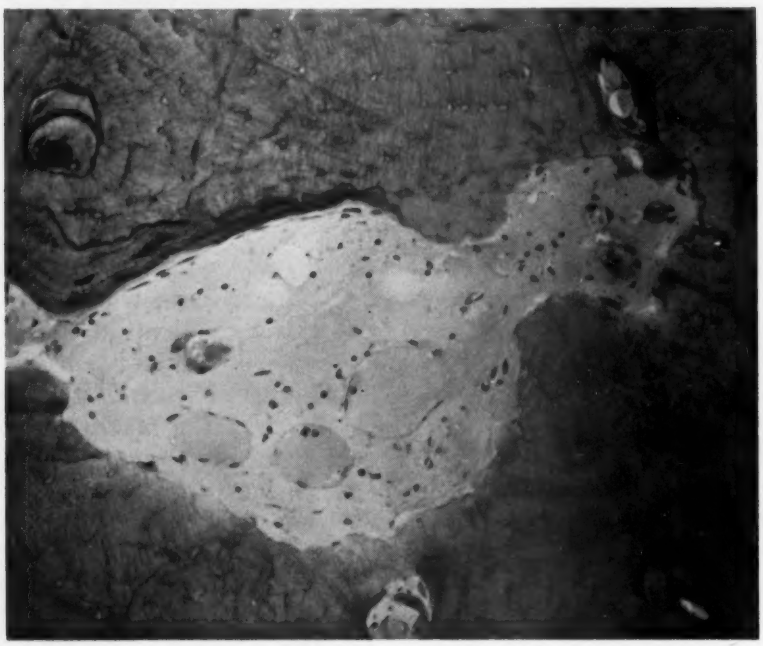

FIG. 13. This is a photomicrograph of the area of resorption. There are blood vessels in the upper right segment. These are just to the left of the center of the large central segment. Note the bone deposition in the haversian system in the left superior corner of the photograph. There may have been bone resorption at one time with two different periods of bone deposition. There was no evidence of active bone deposition in these sections.

Fig. 14. This is an undecalcified section from the same section as in Figure 15. Note that the diameter of the destroyed bone is about 3–6 times the diameter of the haversian systems. The central canals of the haversian systems have a considerable variation in size.

study of bones of this patient, areas of transition in which both radium concentrations and bone destruction were present were infrequently found. In detailed autoradiographic studies, also, radium concentrations were found both in the absence and in the presence of bone destruction (Fig. 22). Little or no radioactivity was found in the atypical osseous tissue in these studies. This may be significant for two reasons, first, the presence of atypical osseous tissue does not appear to be the direct result of ionizing radiation; and secondly, in animal studies with radium and other bone-seeking radio-elements it is considered that malignancies develop in or around the atypical osseous tissue and proliferative fibrous connective tissue. However, the possibility of the radio-elements producing the pathologic and genetic changes and being removed cannot be excluded. Histologic studies also indicate (Fig. 13) that periods of bone resorption may occur which may be followed by periods of bone formation in the same haversian system. If this is true, the relation between radium deposition and pathologic change

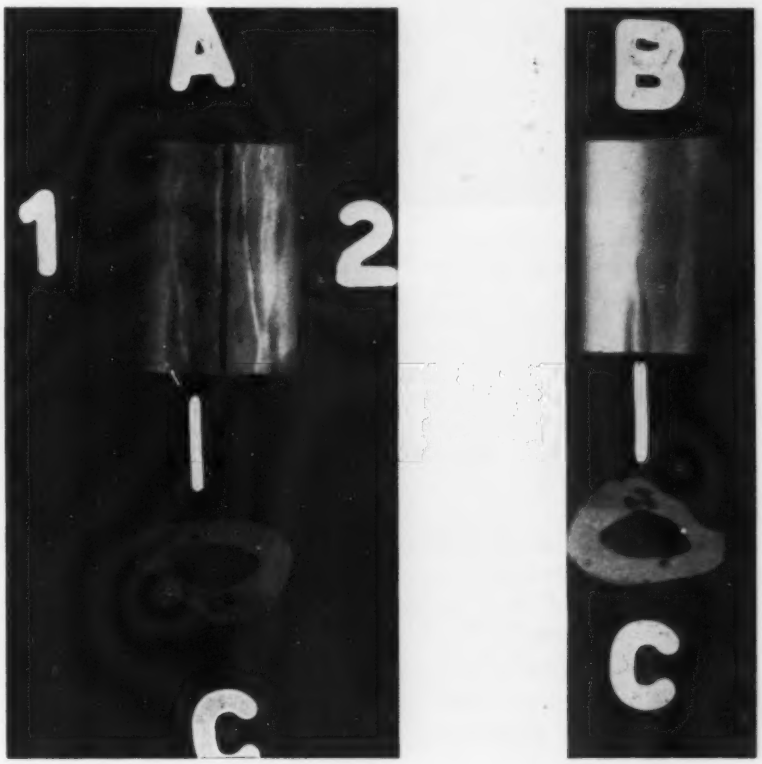

Fig. 15. These are roentgenograms of horizontal and vertical cross sections of the fibula. Note the small "streaked" areas of decreased density in the vertical section appear as well differentiated areas of destruction in the cortex in the horizontal segment. The histological section in Figure 14 shows the two "streaked" areas of destruction which are seen above and below the pointer.

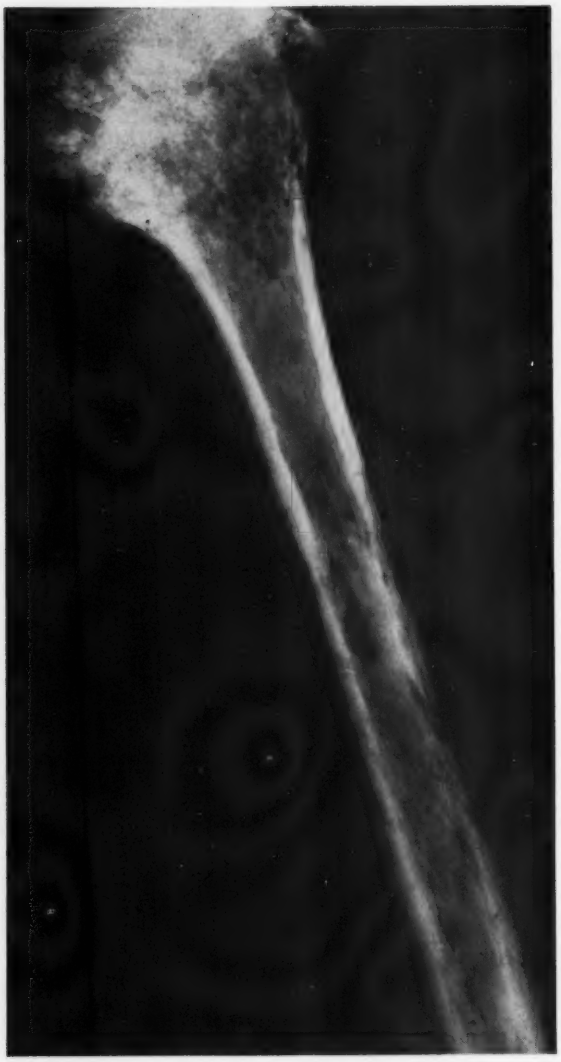

FIG. 16. This is a roentgenogram of the humerus. Sections from it were used in the roentgenographic, autoradiographic and histopathologic studies shown in the preceding figures. Note the areas of decreased density in the shaft and the areas of increased density in the head. These skeletal roentgenographic changes are considered to be characteristic of radio-element deposition. Similar changes may occur following plutonium and strontium deposition.

appears to be a dynamic one in which permanent alterations occur only when the balance between the reparative and destructive processes is disturbed.

In view of these observations it is considered that radium does not always produce pathologic alterations and malignant tumors from the direct effect of ionizing radiation. It is considered that radium deposited in the skeleton usually initiates a sequence of events that eventually results in pathologic changes. These changes may be the end result of augmenting factors such as trauma, damage to blood supply, decreased bone repair, hormonal imbalance, etc. It is reasonable to assume, therefore, that when the destructive effects of radium and other deleterious factors become greater than the reparative processes of the skeleton, permanent alterations occur.

SUMMARY AND CONCLUSIONS

1. A detailed skeletal autoradiographic, histopathologic, radiochemical, and roentgenographic study of autopsy specimens was made on an individual who died at the age of forty-eight years from a fibrosarcoma of the foot and who had received radium water orally at the age of twenty-six years for migratory polyarthritis.

2. Radium was found to be irregularly distributed in small, highly-concentrated areas in compact and cancellous bone, twenty-two years after the administration of radium. In cancellous bone the areas of concentration were usually 5 to 15 microns in the greatest dimensions. There was, however, a wide variation in the size and shape. In compact bone, only about 10–15 per cent of the haversian systems contained marked concentrations of radium.

3. Atypical osseous tissue was found adjacent to the trabeculae in some areas of cancellous bone. The atypical osseous tissue resulted in areas of increased density on roentgenographic examination.

4. There was a wide variation in size of the central canals of the haversian systems in some areas of compact bone while in other areas occlusion of the central canals with a material similar to the atypical osseous tissue was present. Macroscopic areas of destruction of compact bone were found which were usually 1 to 2 mm. in width and 5 to 20 mm. in length. These macroscopic areas of destruction resulted in small,

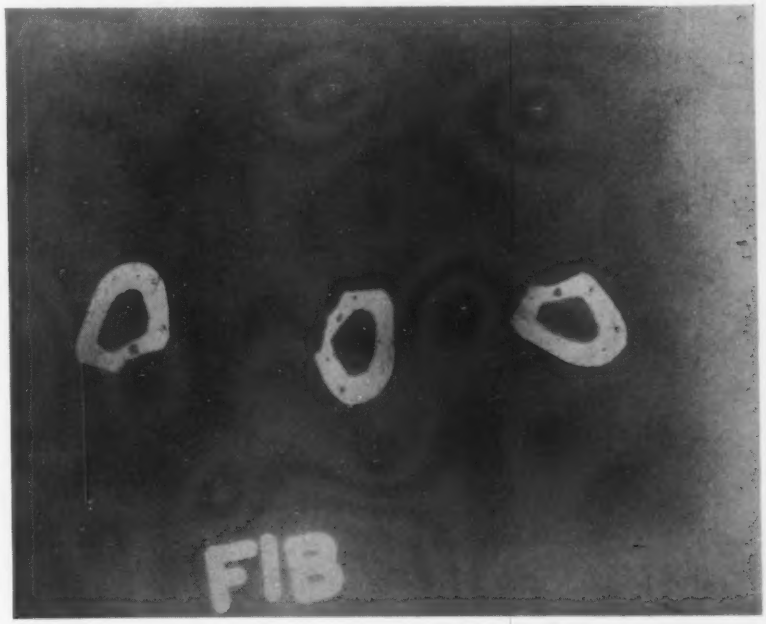

FIG. 17. This is a roentgenogram of three serial sections of the fibula. Note the areas of destruction in the middle of the cortex.

well-differentiated areas of decreased density on roentgenograms.

5. On microscopic examination of the serial bone sections there was minimal evidence of bone regeneration.

6. In most instances there was little or no radioactivity found in the atypical osseous tissue and around the macroscopic areas of bone destruction. Radium concentrations were found as often in the absence as in the presence of bone destruction. For these and other reasons it is considered that radium deposited in the skeleton does not always produce skeletal changes and malignant tumors by the direct effect of ionizing irradiation. Permanent skeletal alterations are probably the end result of the destructive effects of radium and many augmenting factors such as impairment to blood supply, etc.

7. Malignant tumors are considered to develop in or around the atypical osseous

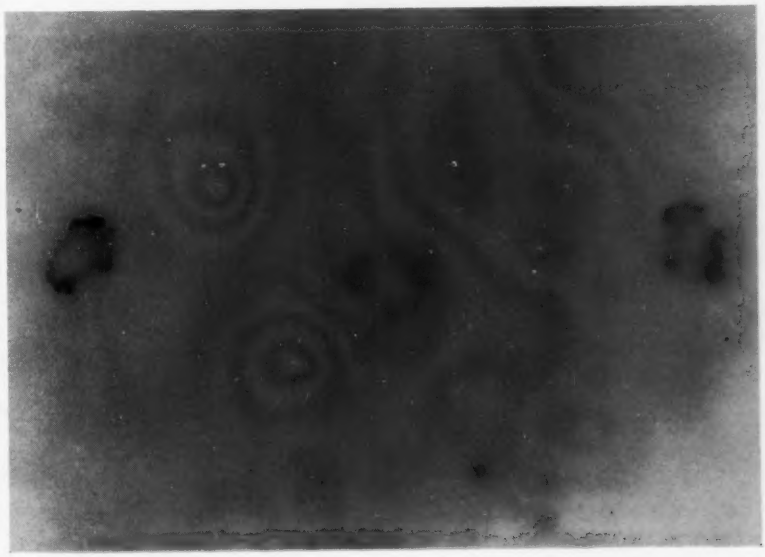

FIG. 18. This is a gross autoradiograph of the three sections of tibia (Fig. 17) showing the small focal concentrations of radium. Note that the concentrations are near the periosteum while the areas of destruction were in the middle of the cortex. None of the destroyed areas coincided when the gross autoradiographs and roentgenograms were superimposed.

FIG. 19. This is a reproduction of a roentgenogram of the foot taken in 1948. Note the area of decreased density in the tarsal scaphoid. At this time a diagnosis of aseptic necrosis was made.

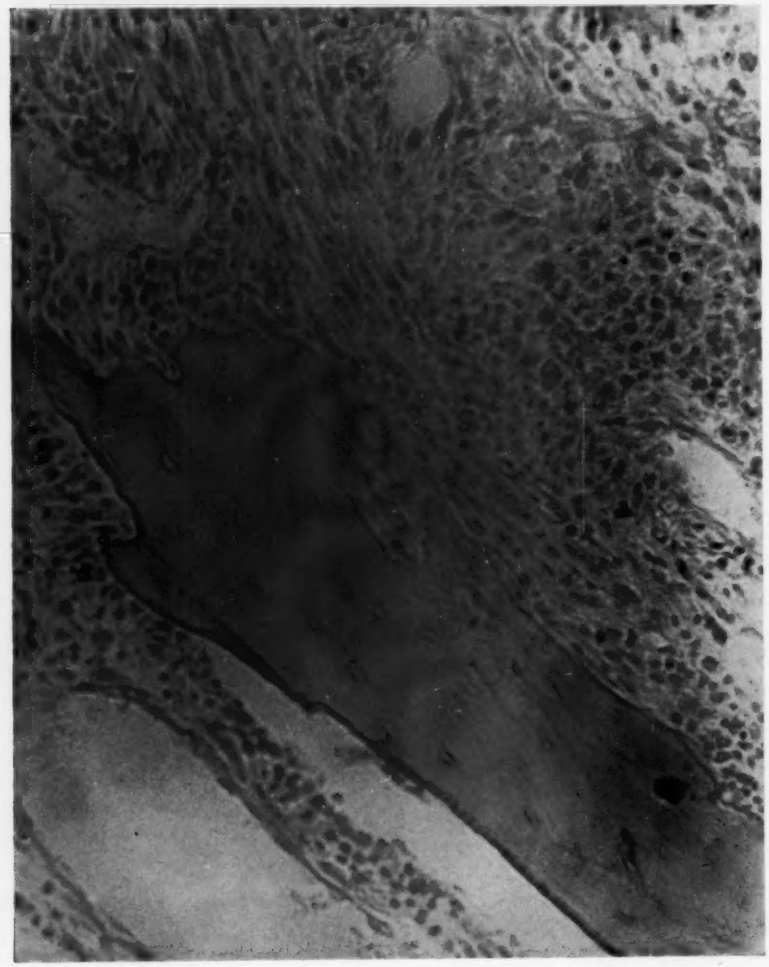

FIG. 20. This is a photomicrograph of a histological section which was made from a biopsy specimen of the foot in 1950. Note the fibrosarcoma destroying the trabecula.

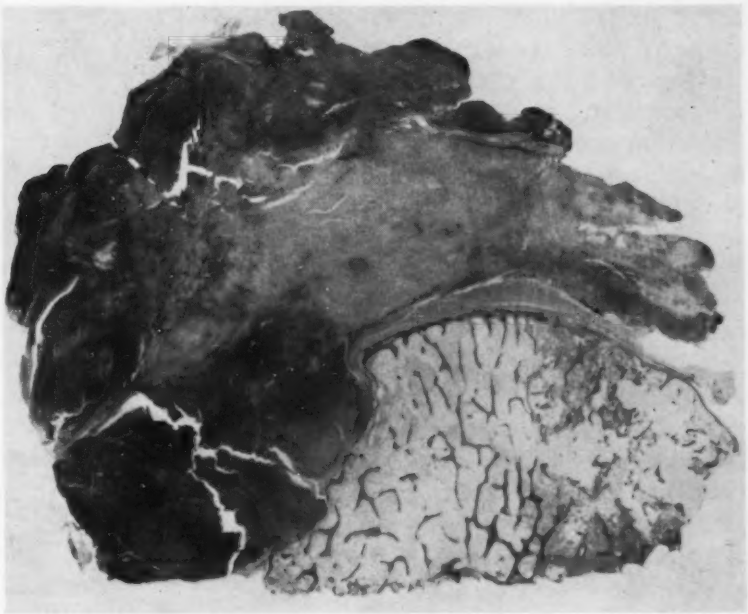

Fig. 21. This is a photograph of a histological section taken from the tumor area in the tarsal bones of the foot following amputation in 1951. Note the invasion of the tarsal bone on the left by the tumor. The trabecular spaces on the lower right are filled with fibrosarcoma.

Fig. 22. This is a roentgenogram of the foot taken prior to amputation in 1951. The tarsal scaphoid has been completely destroyed. Note the marked destruction of the other bones of the foot. The radium concentrations found on radiochemical analyses are about the same. Fibrosarcoma was found in the amputated tibia and a sarcomatous lesion developed on the end of the stump. (The radium concentrations were expressed as curies per gram of dried bone.)

tissue and proliferating fibrous connective tissue following the administration of bone-seeking radio-elements. This abnormal tissue seems to remain dormant but once transition occurs, either a rapid spread or multiple sites of tumor origin develop. Neoplastic tissue was found widely disseminated throughout the specimens examined in this patient.

8. Pain in the foot was the first symptom from the malignant tumor, and a roentgenographic diagnosis of aseptic necrosis of the tarsal scaphoid was made six months later. Three years later a diagnosis of fibrosarcoma of the foot was made on histologic examination, and the leg was amputated. The patient died, four years after the onset of pain in the foot, from multiple metastases of the fibrosarcoma.

9. Since histopathologic changes, similar to those found here, have been found in animals following radium, strontium, plutonium, and yttrium administration, it is considered that the skeletal roentgenogram will probably prove to be a reliable clinical means for the early detection of radio-elements that are deposited primarily in the skeleton.

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The fellowship was carried out under the guidance of Dr. A. M. Brues, director of the Division of Biological and Medical Research, Argonne National Laboratory, 1950–1952.

The author would also like to express his appreciation to W. P. Norris and T. W. Speckman for their assistance and cooperation in the radiochemical analysis, to Miss L. A. Woodruff with whom the autoradiographic studies were conducted, to Dr. J. S. Arnold for his assistance in detailed autoradiographic studies, to Dr. C. H. Hatcher and the late Dr. Dallas Phemister for their assistance and aid in the interpretation of the histopathologic findings, to Dr. J. A. Davis, the attending physician during the terminal illness of the patient for his excellent cooperation and assistance, to Drs. P. C. Hodges and R. M. Potter for their assistance in the interpretation of the roentgenogram and to Dr. R. J. Hasterlik for his assistance in the roentgenographic studies.

The author is indebted to Mr. Atlee Tracy, of the Argonne National Laboratory and Mr. J. T. Stringer of the Naval Medical School for the photographs. The histologic sections were prepared by the Division of Orthopedic Surgery, University of Chicago.

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Vol. 75, No. 3

A COMPARATOR CHAMBER FROM COMMERCIALLY AVAILABLE COMPONENTS*

By E. DALE TROUT, B.S., D.Sc., JOHN P. KELLEY, B.S., ARTHUR C. LUCAS, B.S., *and* EDWARD J. FURNO, B.S.

MANY of the radiation data necessary to medical application of roentgen rays are of a comparative nature. These involve a ratio or percentage evaluation of a roentgen ray beam wherein the ratio expresses some modification of the beam. When a single ion chamber is used for all measurements, great care must be used in monitoring the beam, otherwise voltage or current variations may alter conditions leading to errors when subsequent data are related to the unmodified beam. Any system that makes possible a simultaneous comparison lends itself to more dependable information and should be quite useful in many radiologic departments.

In 1945 L. A. W. Kemp described a system wherein the signals from two ion chambers could be compared directly with one another, the ratio being read on a capacity voltage divider. Kemp's first use of the comparator device was in comparing a radon seed with a radium source of known strength.

In June of 1946 Kemp described the instrument in greater detail and discussed its use for a variety of measurements. Later in 1946 he described its application to an automatic isodose plotter.

Any of us who saw the comparator in use in Kemp's laboratory or in other places in Great Britain could not fail to be impressed with the usefulness of the instrument. Following Kemp's description of it, the original design or some modification of it has been used by a number of investigators. Greening used it to explore scattering in a phantom. Mauchel, Epp and Johns developed and described a completely automatic device of high precision which they have used for dosimetry studies.

In our laboratory we had need for a comparator for use in development and application work. Our needs did not appear to justify an automatic plotter because our problems were so varied and not such as to require the device for continuous use.

We had two Victoreen Ratemeters and a Victoreen Radacon which were used for a wide variety of measurements. They have been found to be dependable within the accuracy needed for most of our work. They have the advantage of availability of a wide variety of chambers for use with the instrument.

Since the Ratemeters were available, we thought it worthwhile to consider their use rather than build a complete comparator consisting of two d.c. amplifiers with associated chambers, etc. The construction of such devices is not inexpensive and getting such a system working is not a simple matter unless considerable electronic and shop talent is available.

What has been done is to take two Victoreen Ratemeters and feed the outputs into a simple null indicator. Figure 1 shows the equivalent circuit. The only modification of the Ratemeters is the addition of a double-pole, double-throw switch to permit the output signal to be fed into the r/minute meter of the Ratemeter or into the comparator. The mounting of this switch

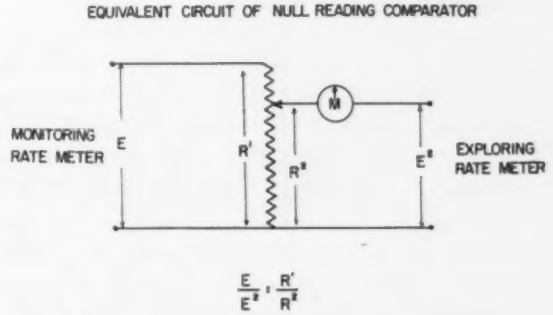

FIG. 1. Equivalent circuit of comparator.

* Presented at the Thirty-seventh Annual Meeting of the American Radium Society, Washington, D.C., April 21–23, 1955.

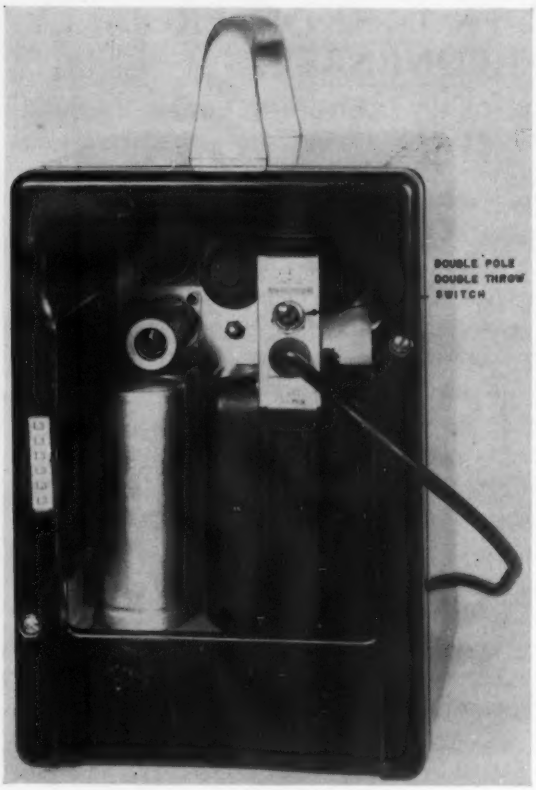

FIG. 2. Photograph showing double-pole, double-throw switch on Ratemeter.

involves no machine work or alteration of the chassis or its wiring. The only wiring changed is the two leads to the meter. The switch is mounted on a plate attached to the power transformer (Fig. 2).

With the possible exception of the zero-center meter, all the components for the indicator can be obtained from an electronic supply house. The output meter of the Victoreen Ratemeter is a 0–100 microampere instrument, and a 150–0–150 microampere galvanometer obtainable from an instrument manufacturer or scientific supply house could be used. This would be safe in case a careless operator permits the full current from the rate-meter to flow through the galvanometer. The more sensitive the meter the more accurately the ratio can be read. We have used a 25–0–25 microampere meter without difficulty. The procedure followed which prevents overloading the meter upon initial radiation exposure is to position the chamber in the roentgen-ray field and adjust the Ratemeter scale selectors to obtain approximately equal scale deflections on the Ratemeter output meters. The comparator is then set to 100 per cent with the zero adjust potentiometer at about mid-scale. The output of the Ratemeter is then switched to the comparator with the roentgen ray off. The roentgen ray is then turned on and the comparator balanced to zero using the zero adjust potentiometer.

In Figure 3 is shown the circuit diagram for the comparator. The nine 300-ohm

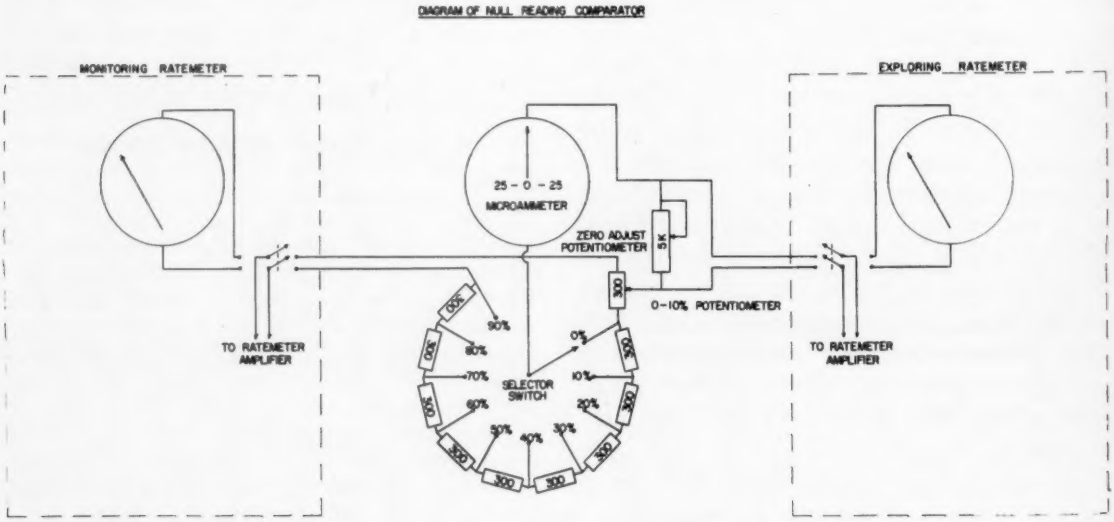

FIG. 3. Circuit diagram of comparator.

fixed resistors are 1 per cent precision resistors. The 300-ohm potentiometer is wire-wound and is selected for accurate linearity. The total resistance of the resistor chain was made 3,000 ohms to match the resistance of the output meter of the rate-meter. The 5,000-ohm zero adjust potentiometer is wire-wound but need not be a precision or selected type. This value was chosen to obtain sufficient latitude to zero the comparator under all operating conditions.

A photograph of the comparator is shown in Figure 4. Figure 5 is a photograph of the back of the comparator showing: (1) The input from the monitoring and exploring rate-meters; (2) the knob for the zero adjust potentiometer placed on the back of the cabinet to minimize the chance of its being accidentally moved after adjustment; (3) a switch permitting the comparator current to be fed to a projection galvanometer if the device is to be used for teaching or demonstration to a large group. This double-pole, double-throw switch is not shown on the circuit diagram of Figure 3.

The only precaution that must be observed in using the Victoreen Ratemeters is that the Ratemeters and the comparator must be placed on a nonconducting surface and the cases must not make electrical contact with one another. This is made necessary by the fact that the output meter in the Ratemeters is not at ground potential and, from one Ratemeter to another, the meter may not be at the same potential with respect to ground. This difference in potential which may exist between two instruments sets up a circulating current when the cases are connected. We have noted a difference in potential of 0.6 volt between two of our instruments. Under these conditions it is not possible to adjust the comparator to zero with no radiation to the chambers.

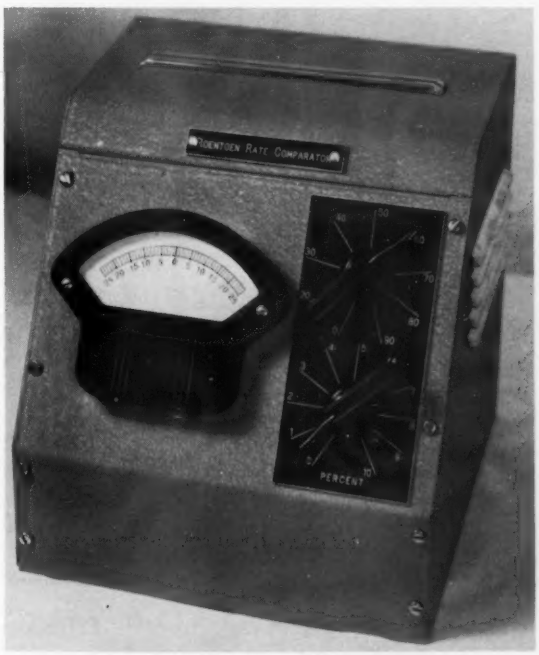

FIG. 4. Photograph of front of comparator.

FIG. 5. Photograph of back of comparator.

This same precaution must be exercised for the metal bodies of the two probes which must not be electrically connected. This is easily accomplished by using conventional laboratory clamps with rubber covered jaws.

These are the only special precautions we have found necessary. We are presently using two Ratemeters and a Radacon in any combination depending on which instruments are available at the time.

One of the uses to which we have put the

FIG. 6. Photograph of isodose plotting board showing Ratemeters, comparator, and master Selsyns.

comparator is the plotting of isodose curves. In this application the monitoring chamber is positioned at the surface of a water phantom and the exploring chamber remotely positioned using a Selsyn drive. The plotting board, comparator, Ratemeters, and master Selsyns are shown in Figures 6, and the water phantom, probes, and slave Selsyns are shown in Figure 7. A spot of light is projected on the glass plotting board to indicate the position of the exploring chamber in the water phantom. The sides of the water phantom are clear plastic of approximately unit density. This perimts the use of either vertical or horizontal roentgen ray beams as shown in the block diagrms of Figures 8 and 9. The comparator is set for the percentage isodose line to be plotted and the exploring probe moved in the roentgen-ray field obtaining zero balance points on the comparator. In practice, balance points are obtained every 1 to 5 mm. near the edge of the roentgen-ray field and every 5 to 10

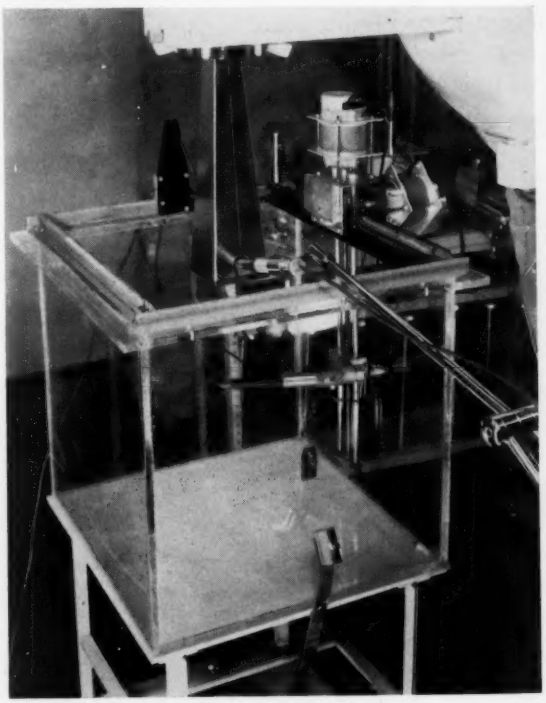

FIG. 7. Photograph of water phantom with probes and slave Selsyns.

mm. inside the projected direct reontgen-ray field and the points marked on centimeter tracing paper placed on the plotting board. A line is then drawn through the points of equal percentage depth dose. In a similar manner all other lines of equal percentage depth dose can be obtained. For a 10 by 10 cm. field at a half-value layer of 3.0 mm. Cu, a complete set of isodose curves can be made in about one half hour.

The percentage depth dose at any location in the water phantom can be obtained by adjusting the comparator to zero with the exploring probe positioned at the desired location and reading the percentage depth dose directly from the comparator dials.

Another use for the comparator is in plotting transmission curves in various materials. A remotely controlled mechanism can be used to change the thickness of filter material in the roentgen ray beam. Such a filter changing device, shown in Figure 10, was made using a television antenna rotor mechanism. A master Selsyn was geared to the antenna rotor to give an accurate indication of the position of the changer mechanism. The slave Selsyn is housed in the control box and the dial is graduated in degrees, radians, and filter slot positions. Figure 11 shows the remote control drive and position indicator. To use this device an open slot is placed in the beam and the comparator adjusted to 100 per cent. The filter changer is then rotated until the first thickness of material is in the roentgen ray beam. The comparator is adjusted with the percentage selectors until a null reading is obtained and the percent transmission read off the dials. This procedure is repeated for each of the

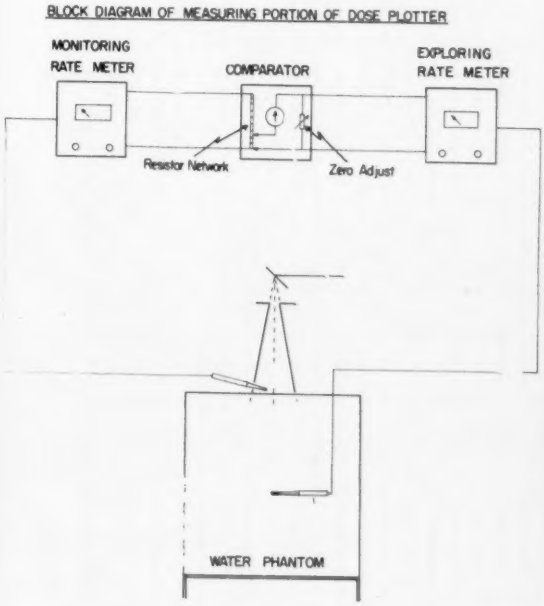

FIG. 8. Block diagram of arrangement for plotting with vertical roentgen ray beams.

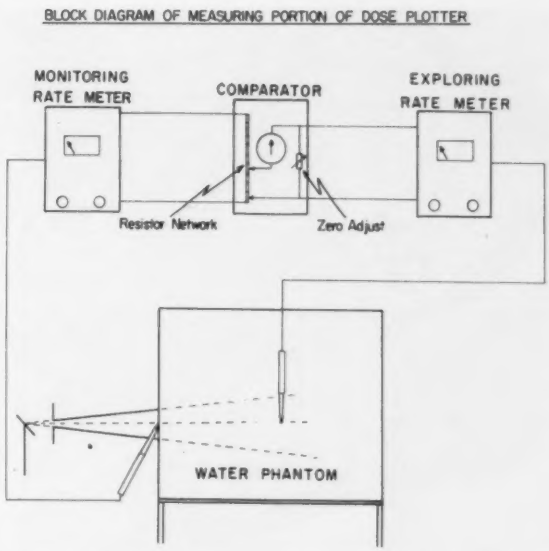

FIG. 9. Block diagram of arrangement for plotting with horizontal roentgen ray beams.

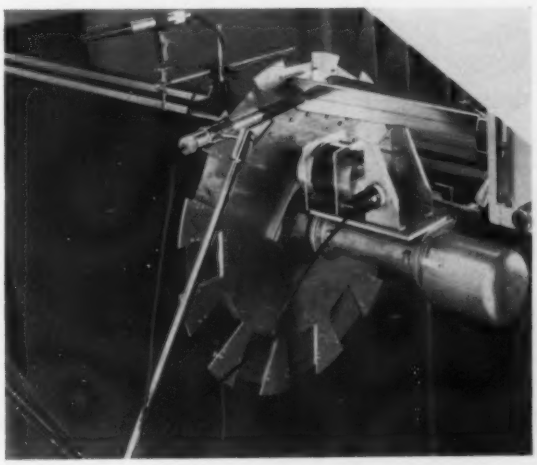

FIG. 10. Photograph of filter-changer.

FIG. 11. Photograph of control for filter-changer.

various thicknesses of absorber. These data can be plotted as a transmission curve. Figure 12 shows a plot of a copper transmission curve obtained in this manner. Eleven points were determined for this curve and the time required was as follows: (1) to get out of cabinets and set up the comparator, filter changer, and position tube and probes—ten minutes; (2) to take the data and plot the curve—five minutes.

The comparator is also useful in plotting the field distribution from a roentgen tube. For plotting distribution on a plane with fields not exceeding 30 cm. in diameter, the probes can be mounted on the isodose plotter with the water removed from the plastic tank. The Selsyn system is then used to position the chamber remotely across the roentgen-ray field and the percentage of the central beam intensity read directly from the comparator dial settings.

If the field distribution on an arc is to be plotted, the rotor-Selsyn arrangement is used and the filter holder replaced with a 50 or 100 cm. arm as shown in Figure 13. The monitoring chamber is placed at some point in the roentgen-ray field and the comparator balanced to 100 per cent with

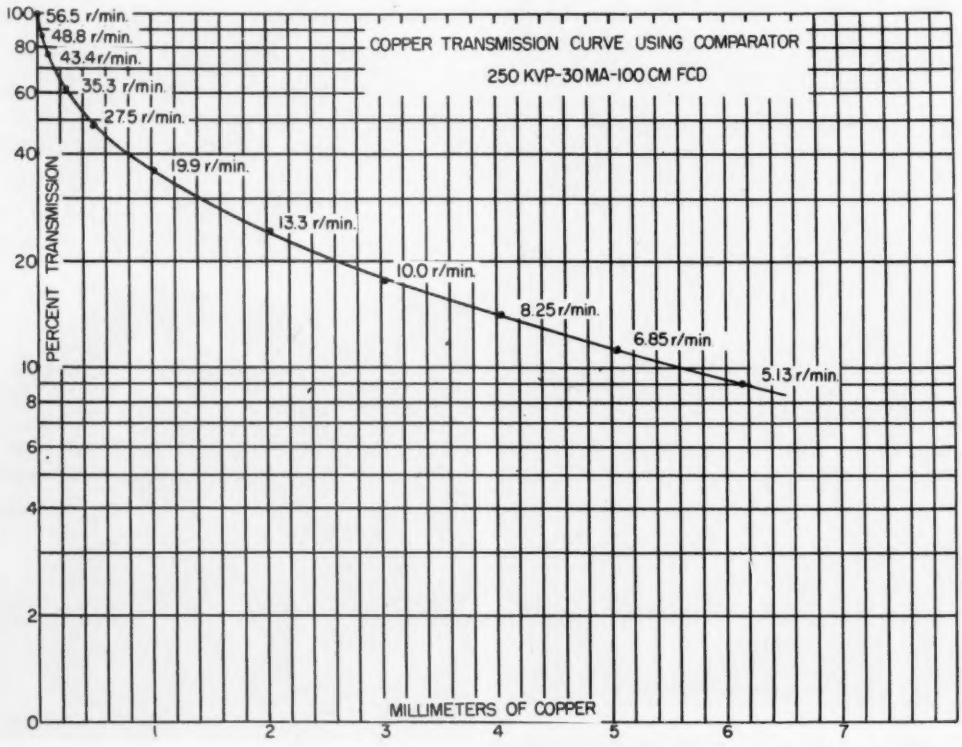

FIG. 12. Copper transmission curve.

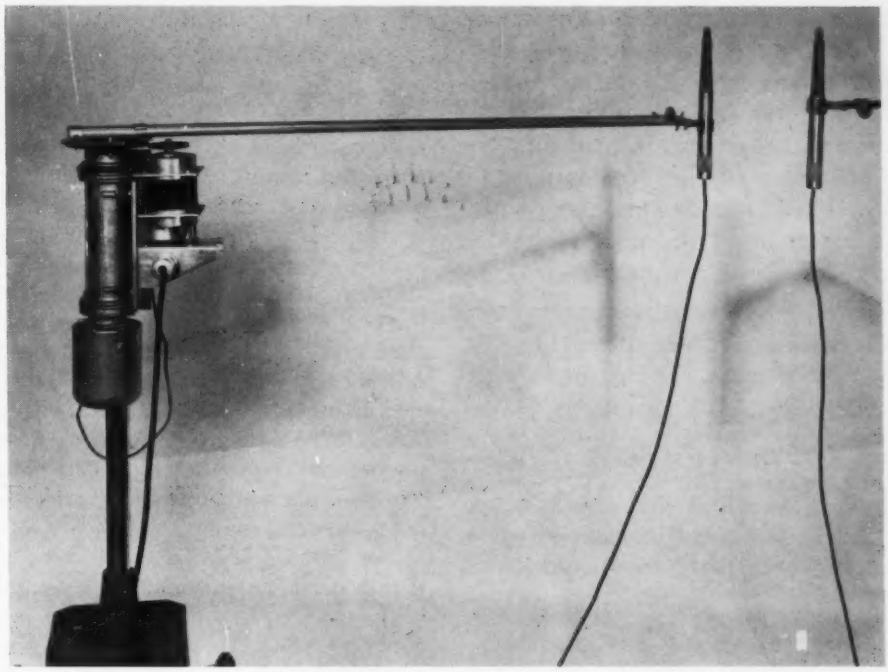

FIG. 13. Photograph of field plotter.

the exploring chamber at the point of reference. The exploring chamber can then be moved through the beam and relative dose-rates read on the comparator. Field distribution taken in this manner along the roentgen tube axis through 165° on a 2,000 kv. (peak) unit is shown in Figure 14.

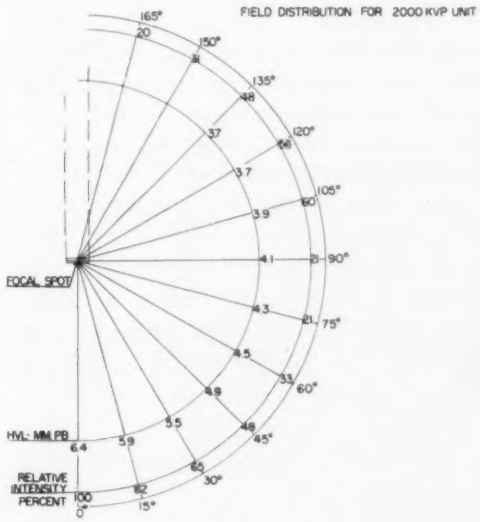

FIG. 14. Field distribution for 2,000 kv. (peak) unit.

In some instances the point of maximum dose-rate in a roentgen-ray field may not be known. In such instances the exploring rate-meter can be switched to its r/minute scale and the location of maximum dose-rate determined. A plot of field distribution taken during the development of a 250 kv. (peak), 360° copper window tube obtained in this manner is shown in Figure 15.

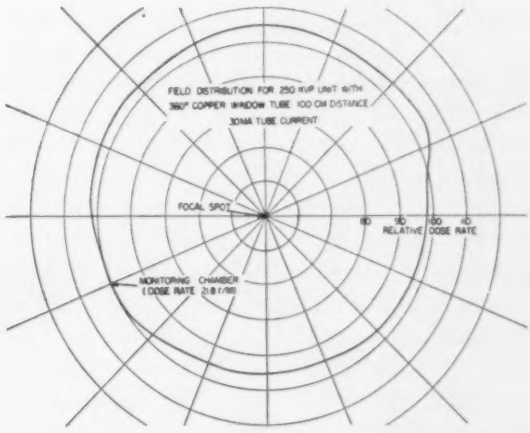
FIELD DISTRIBUTION FOR 250 KVP UNIT WITH
360° COPPER WINDOW TUBE 100 CM DISTANCE
30MA TUBE CURRENT
FOCAL SPOT
RELATIVE DOSE RATE
MONITORING CHAMBER

FIG. 15. Field distribution for experimental 360° 250 kv. (peak) copper window tube

If, at any time in the course of taking data, it is desired to obtain absolute rather than relative readings, the output meters of the Ratemeters can be switched back in the circuit and the dose-rate read directly.

These are some of the applications for which we have found the comparator useful. It has reduced the time for taking data to a fraction of that required by previous methods.

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DISCUSSION

DR. LAURISTON S. TAYLOR, Bethesda, Maryland. I find Dr. Trout's presentation of great personal interest. Having myself been in the radiation measurement game for thirty years, I am well aware of the difficulty in making a long series of measurements, such as depth dose or attenuation measurements, where it is necessary to relate all of the readings back to some standard reading. In our own laboratory, we have in the past spent many hours of peoples' time simply setting and controlling the output of a roentgen-ray machine over a long series of measurements. The system described by Dr. Trout will eliminate the necessity for doing this under a large number of circumstances. With manpower at a premium today, this is a particularly important item.

The general idea of a monitoring chamber tied into the measuring chamber is not particularly new. On the other hand, such systems frequently run into considerable complication. The arrangement by Kemp, and modified by Dr. Trout, represents a distinct contribution to our measuring techniques.

The other item that I find of particular interest in his report is the fact that his entire system is made up of components that are commercially available. This means that one does not need to go into a lot of elaborate shop work and instrumentation in order to achieve a result. By using conventional equipment in a new way, it is possible to develop substantially more economical radiation measuring set-ups.

Dr. Trout's laboratory has already turned out an immense amount of useful information for the radiotherapist and diagnostician. I feel certain that with this type of equipment available in their laboratory, we are going to continue to see a steady stream of this important information being made available to the public.

VOL. 75, NO. 3

SKIN CANCER: CORRELATION OF FIELD SIZE AND CANCEROCIDAL DOSE IN ROENTGEN TREATMENT

By KENNETH D. A. ALLEN, M.D., *and* JOHN H. FREED, M.D.*
DENVER, COLORADO

THERE is a gap in the teaching and radiologic literature about skin tolerance of cancerocidal doses of roentgen rays, depending on the size of the field irradiated. This presentation furnishes data on this subject derived from correlating the skin effect in terms of cosmetic results shown in 1,013 private cases treated for carcinoma of the skin and lip by roentgen rays. It also includes data on the effect of fractionation of the total roentgen dose. Interest in this phase of dosage has been generated by Strandqvist,[4] Andrews,[2] and Ahlbom.[1] Graphs showing tolerable skin dosage, both fractionated and massive, are presented in 564 cases segregated according to the size of field treated. It is relatively easy for us arbitrarily to prescribe roentgen dosage for an observable, palpable and measurable skin cancer because of memory of our previously treated cases, but this is more difficult for those with less experience and without old case records for reference. Unfortunately there is no accepted biologic unit which correlates the number of roentgens, quality of radiation, fractionation of radiation, size of field and tissue response.

METHOD OF STUDY

A pathologic diagnosis of either basal cell or squamous cell cancer was made by biopsy in 736 of the original cases. No biopsy was obtained in the others because the lesions were clinically so obviously cancer, or because we wished to avoid the mild residual dimpling of the scar produced by biopsy in order to get the very best cosmetic result. Many of the latter were in younger women, where the cosmetic result was of prime importance. Biopsy was not done in other cases because the referring physician requested that no biopsy be made, feeling the diagnosis of cancer definite and biopsy an unnecessary expense for the patient.

The majority of these skin cancers were treated with 90 kv. to 125 kv. radiation, with half-value layer varying from 1 mm. Al to 5 mm. Al, except for a very few that were treated with 135 kv. radiation, half-value layer 6 mm. Al. Twelve were treated with 200 kv., half-value layer 1 mm. Cu and 13 with 250 kv., half-value layer 1.5 mm. Cu. One patient with a very large lesion was treated with 1,000 kv., half-value layer 3 mm. Pb. We frequently use the single massive dose technique to treat small lesions not over 1 cm. in diameter on patients in a remote cancer clinic that we visit only one day each month and also for the convenience of patients living at some distance from Denver who come to our office for treatment. We have recorded the cosmetic results in all cases, grading them 1 through 4. There was no indication that fractionation improved the cosmetic result in cases with field size under 1 sq. cm. The usual procedure in our office and home hospital for small lesions, under 1 sq. cm. in size, is to photograph, biopsy, and administer 1,500 r then wait a day for a paraffin section pathologic report. If cancer is reported we give an additional single treatment of 2,800 to 3,200 r and send the patient home, to return at intervals for our routine follow-up. In lesions requiring fields from 1.2 (1.15 sq. cm.) to 2.8 cm. in diameter (6.2 sq. cm.) biopsy is done and 1,000 r given. If cancer is reported, two more doses of 1,100 r each on alternate days are given, yielding a five-day frac-

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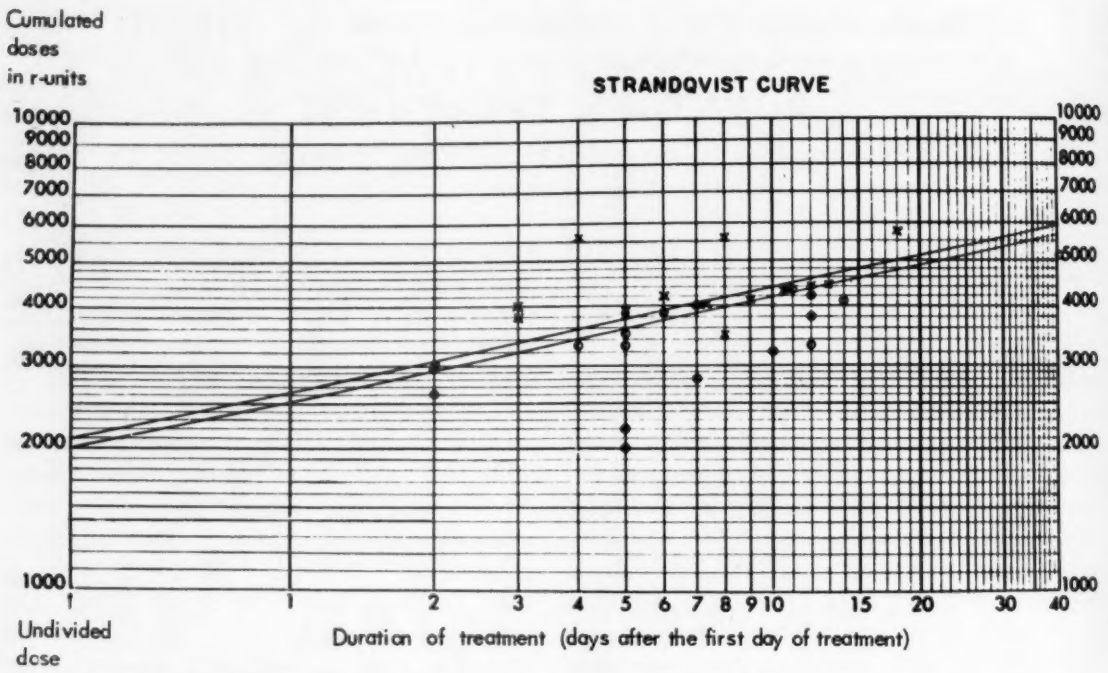

Fig. 1. Strandqvist's curve of massive dose versus actual duration of treatment in days. Note very small range of permissible dosage.

tionation like that advocated by Widman.[5] Thin, flat cancers of this size are treated with 100 kv. and not over 1 mm. Al filter equivalent; thicker lesions are treated with 125 kv. and 1 mm. or more of added aluminum filter.

Large, thick lesions from 6 to 7 cm. in diameter are treated with 250 kv. radiation, half-value layer 1.5 mm. Cu, fractionated over ten to twelve days. We feel that accessibility of 250 kv. therapy apparatus is essential for anyone treating cancer of the skin, particularly large lesions in close proximity to bone or cartilage such as the nose, ear, and, rarely, back of hand. The tumor dose was determined in all of these cases and is the dose referred to hereafter. Air dose, skin dose, and tumor dose are essentially the same in superficial small lessions under 1.2 cm. in diameter and 2 to 3 mm. in thickness. Above this size, the skin dose and tumor dose were calculated according to the backscatter and depth dose data of Glasser, Quimby, Taylor and Weatherwax[3] for the particular size field and quality of radiation used.

Patients with skin cancer are notoriously difficult to follow. In spite of a follow-up system which is very effective for cancer in other parts of the body, only 564 of 1,013 skin cancer cases could be induced to return regularly for a period of one year; only 289 of that number treated more than three years ago could be followed more than three years, and only 146 of that percentage treated more than five years ago could be followed for five years or more.

It was decided to use only the 564 patients (452 in whom biopsy was done) followed one year or more to plot on the accompanying graphs. The 112 unbiopsied cases followed one year or more were included in this study since its primary purpose was to evaluate maximum normal tissue tolerance which would not be altered by the biopsy. In addition, all but 2 of these 112 unbiopsied cases received a radiation dose above the curative dose found by Strandqvist and therefore do not influence the minimum curative dose as evaluated from our series of 452 biopsied cases.

Although a one year follow-up is per-

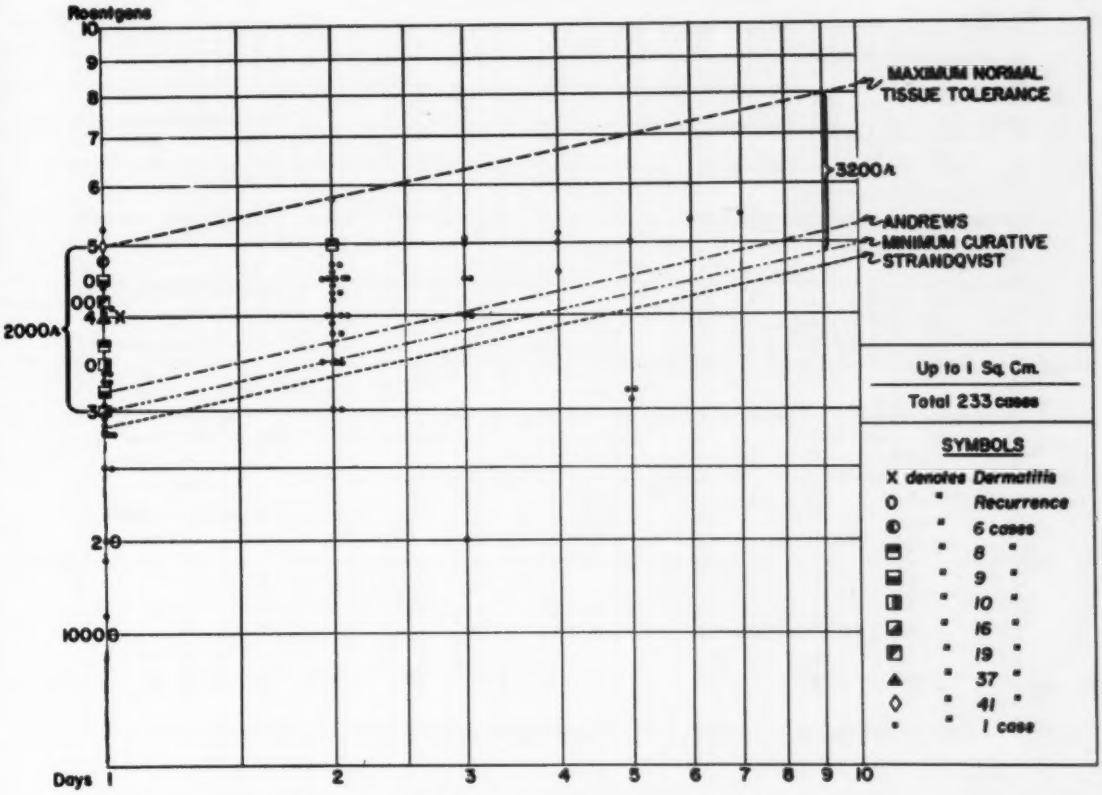

FIG. 2. Results in 233 cases of very small skin cancers treated with fields under 1 cm.² in size. Note large range of permissible dosage which increases with fractionation.

haps not sufficient to evaluate late radiodermatitis in all cases, some sign of permanent damage to the normal skin is evident in our experience during this period of time.

Careful follow-up records are available on all of these 564 patients, with color photographs before and after treatment of a large number. These follow-up records and photographs were reviewed to determine the number of patients having evidence of radiodermatitis (poor cosmetic result) or recurrence. Mild radiodermatitis was considered present when there was evidence of telangiectasis in a residual smooth scar, even though the result was otherwise very satisfactory. Cases in which there was considerable delayed healing or mild late necrosis were considered as severe radiodermatitis.

A graph was made by plotting the tumor dose administered to the lesions in these 564 patients as the ordinate and the fractionation time in days as the abscissa on double logarithmic paper according to the method used by Strandqvist and later by Andrews, differing only in that *day one* is considered the first day of treatment on our graphs, while Strandqvist and Andrews consider the time in days as representing days after the first day of treatment. Different symbols were used, as indicated on the graphs to identify cases in which there were good results, mild and severe radiodermatitis, and recurrence. Using this same method, we next plotted cases on separate graphs according to the size of field irradiated. The following field sizes were segregated in square centimeters: 1 or under, 1 to 2, 2 to 4, 4 to 6, 6 to 9, and over 9 (Fig. 2, 3, 4, 5 and 6). In all of these graphs we found that the slope of the curve indicating the total increase in roentgens required for cure above a single massive dose when fractionating the treatment from two to twenty

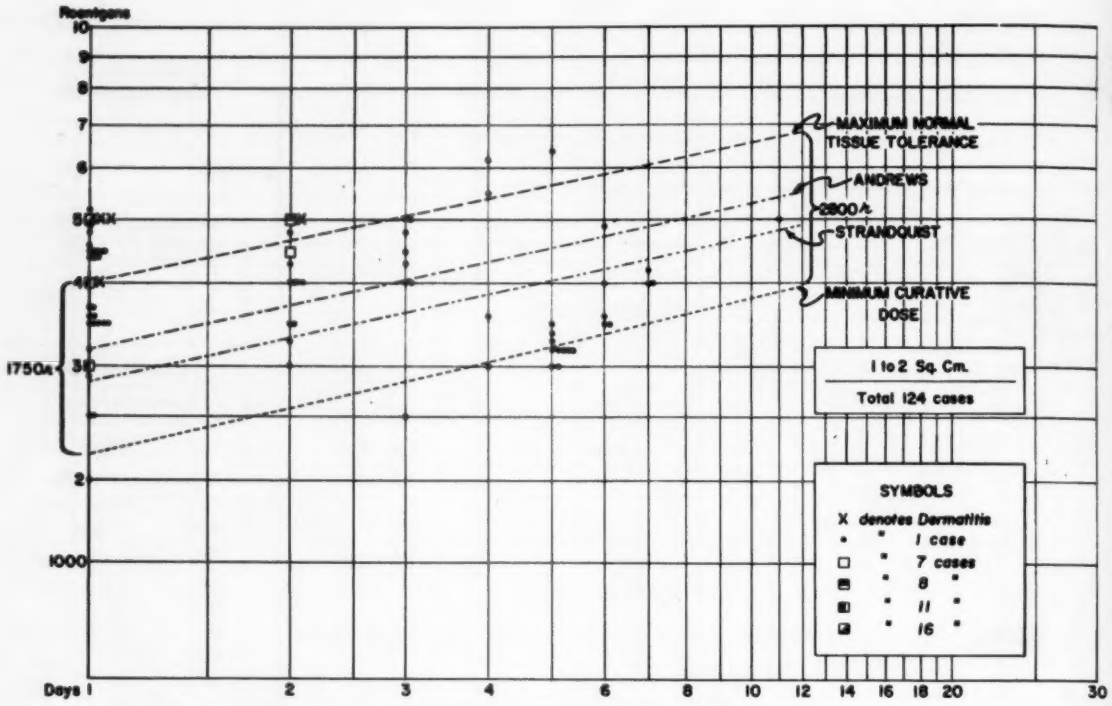

Fig. 3. Results in 124 cases of skin cancer treated using fields of 1 to 2 cm.^{2} in size.

days corresponded to that determined by Strandqvist as shown in Figure 1.

It can be seen from Strandqvist's diagram in Figure 1 that the curve is a straight line on a double logarithmic coordinate system and follows the mathematical equation $De \cdot r = D/t^{0.22}$ where $De \cdot r$ = the equivalent roentgen dose when delivered in a single treatment that will produce the same biologic effect as a roentgen dose D fractionated over a period of t days. For added clarification, the equivalent roentgen dose $De \cdot r$ might be defined *as the single massive dose that has the same biologic effect as that obtained by the cumulative effect of radiation from a fractionated dose D delivered in t days*. The exponential factor 0.22 represents the slope of the Strandqvist curve. The quantity $t^{0.22}$ in the equation may be termed the fractionation factor and can be calculated with the help of logarithms. The fractionation factors for two, three, four, five, six, seven, eight days and so on, will be 1.17, 1.27, 1.36, 1.43, 1.48, 1.54, 1.58, 1.63, etc. Thus, to find the total number of roentgens to use for a given number of days, the single massive dose can be multiplied by the fractionation factor for that number of days. This can also be obtained directly from the double logarithmic fractionation diagrams (Fig. 2, 3, 4, 5 and 6). Through the use of the above equation and logarithmic tables, the equivalent roentgen dose ($De \cdot r$) was determined on 289 of our patients followed for over three years. This dose was plotted as the ordinate against the size of field as the abscissa on plain square coordinate paper as another method of evaluating graphically the results of this study on the effect of field size. This graph is shown in Figure 7.

RESULTS

In this group of 564 cases there were 18 recurrences, all of which were at the margins of the lesions due to the use of too small a field rather than to underdosage. For small lesions we rarely use a field that extends more than 2 mm. beyond the margin of the lesion gradually increasing the width of the margin up to 5 mm. for larger lesions. We believe this policy is justified

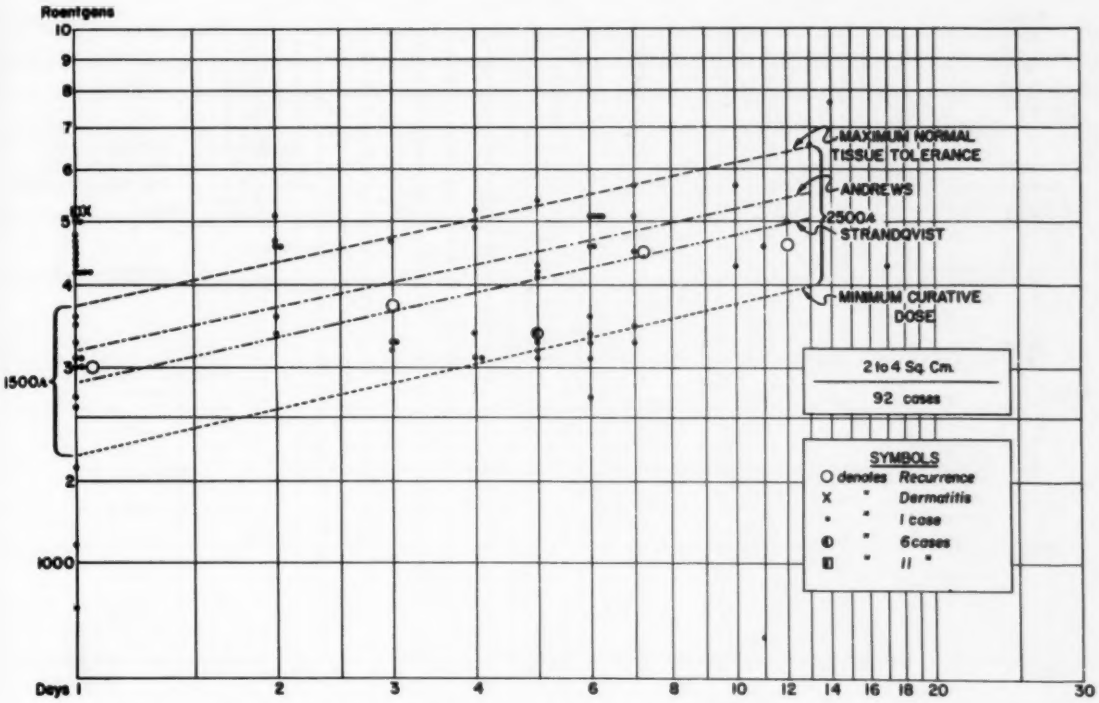

FIG. 4. Results in 92 cases of skin cancer treated using fields of 2 to 4 cm.^{2} in size.

in order to get the best cosmetic result, even though we realize it is attended with some risk of marginal recurrence. The 3 per cent marginal recurrence rate, however, is so small that we do not believe it warrants any change in this policy. Eradicating the recurrences has not been difficult in most instances. There were 24 cases of mild radiodermatitis and 8 cases of severe radiodermatitis. Only 2 of the 8 severe cases were on the face, the others being on the leg, back or hand. An analysis of the results of this study as shown by means of our graphs (Fig. 2, 3, 4, 5 and 6) supports the results as reported by Strandqvist and indicates that the slope of his curve represents reasonably well the cumulative effect of roentgen dosage with time; or, in other words, the total increase in roentgens required when fractionated over a period of days to produce the same biological effect as a single massive dose.

Although our results seemed to support Strandqvist's work insofar as the cumulative effects of radiation were concerned, it was very apparent that the range of safe dosage of 100 r for a single massive dose or 300 r for a dose fractionated over twenty days as shown by him in his graph (Fig. 1) was much too limited and that, depending on the size of field used, a much wider range of dosage could be administered without danger of recurrence or complicating radiodermatitis. The range of safe dosage may be defined as *the difference between the minimum roentgen dose that will result in a cure of a skin cancer and the maximum normal skin tolerance dose or the latitude of dosage that will cure a skin cancer without danger of recurrence or complicating radiodermatitis*. This is directly related to size of field, as shown by the graphs of our studies.

The curve of maximum normal tissue tolerance was established for each size field, as shown in the graphs 2 to 6 inclusive by plotting a curve with the same slope as Strandqvist's curve that passed above or among cases with good results and below most cases of radiodermatitis. In a similar manner, the minimum curative dose curve was established for each size field by

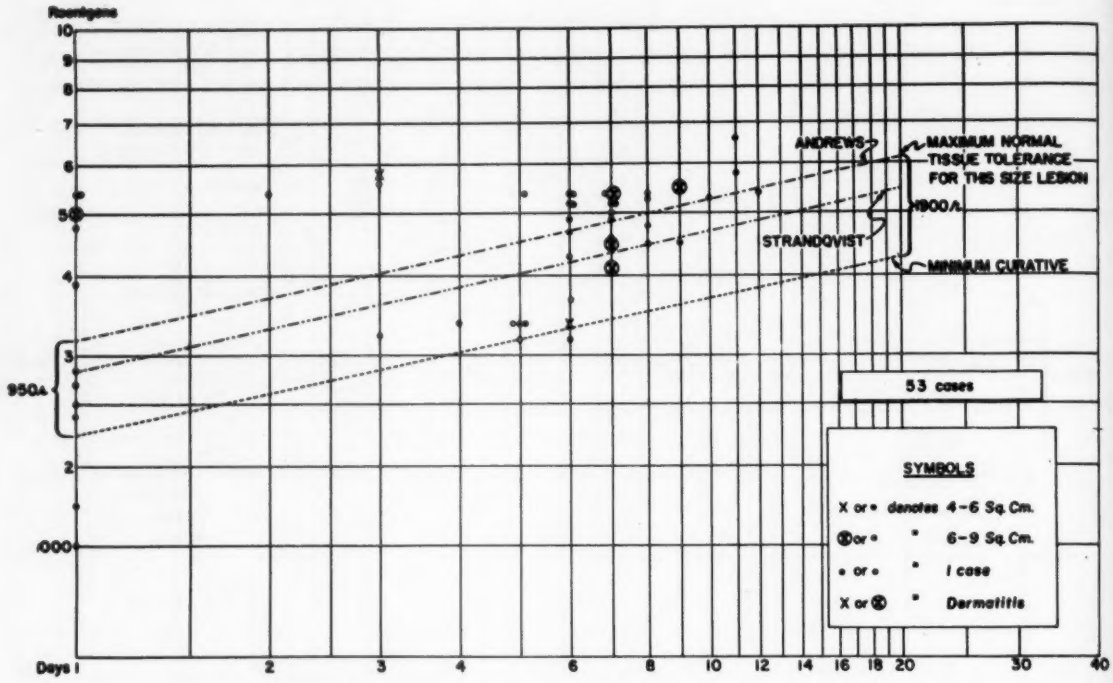

FIG. 5. Results in 53 cases of skin cancer treated using fields of 4 to 6 cm.^{2} and 6 to 9 cm.^{2} in size. Note decrease in range of permissible dose due to increase in size of fields.

drawing in a curve of the same slope that passed through cases cured by the lower dosages used in treatment. The Strandqvist curve and Andrews' modification of the Strandqvist curve are also shown for comparison. It is interesting that for fields over 1 sq. cm. in size our origin is 2,250 r, the same dose that Strandqvist found to be curative for a single massive dose, as mentioned in his discussion, though not shown exactly this way on his graph.

From an analysis of our plotted results shown in Figures 2 to 6, it appears that the latitude of safe dosage for a single massive dose delivered to a small field under 1 sq. cm., for instance, is about 2,000 roentgens. This range of safe dosage increases to as high as 3,200 roentgens if the treatment is fractionated over a period of nine days, which would be expected since it is known that normal skin recovers more rapidly than cancerous skin from the cumulative effects of fractionated radiation and forms the basis for the use of fractionation. It has long been our clinical impression that fractionation increases latitude of permissible dose. The range of safe dosage for a single massive or fractionated dose decreases with increase in size of field, being only 500 r for a single massive dose or 1,200 r if fractionated over a period of ten days for field sizes over 9 sq. cm. The graphs of field sizes between 1 and 9 sq. cm. show latitudes in single massive dose of 1,750, 1,500 and 950 r, respectively, as the fields enlarge. This is further graphically emphasized in Figure 7 by the plot of equivalent roentgen dose versus the size of field. Notice that the occurrence of radiodermatitis is much higher as the field size increases.

COMMENT

The results of our study tend to confirm Strandqvist's work regarding the cumulative effects of fractionated radiation but indicate that a much wider latitude of dosage, either single or fractionated, can be used without danger of recurrence or complications. This latitude of dosage varies

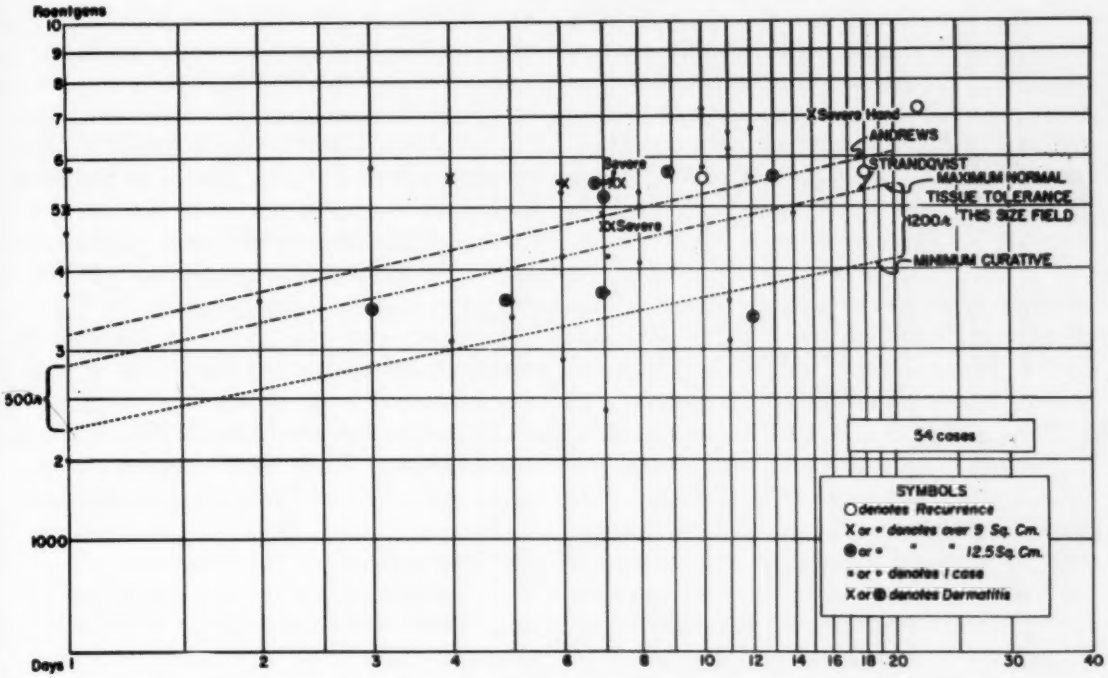

FIG. 6. Results in 54 cases of skin cancer treated using fields of 9 cm.² or more in size. Note great reduction in range of permissible dose which increases somewhat with fractionation.

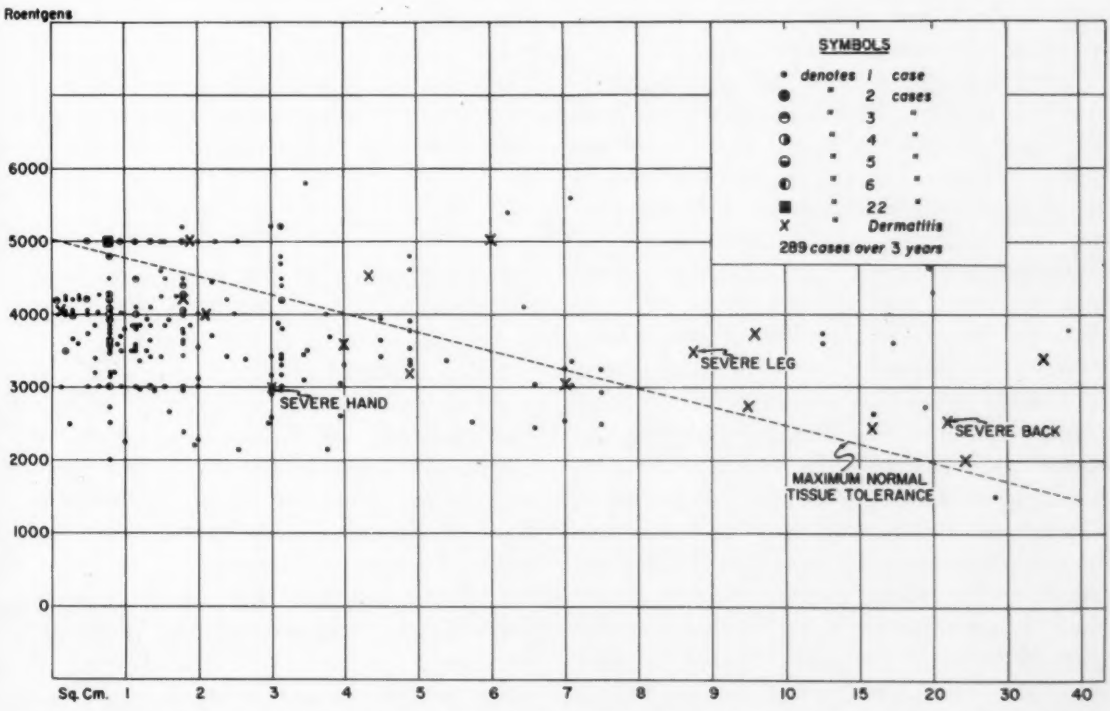

FIG. 7. Graph of curative dose computed on fractional cases into a single irradiation calculated by using the formula $De \cdot r = D/t^{0.22}$ in 289 cases of skin cancer followed for over three years, versus the actual size of fields in each case. This graph integrates dose in roentgens, days of fractionation and size of fields. Note that most cases of radiodermatitis occur in large size fields.

with the size of field irradiated. Analyzing Strandqvist's results we believe his narrow latitude of dosage was due to the fact that he neglected to consider the size of field in evaluating his recurrences and complications. Referring to Figures 1 and 6, it can be seen that for fields under 1 sq. cm. in diameter in our series the *minimum* curative dose, when administered in a single treatment, is about 3,000 r and that for fields over 9 sq. cm. in size the *maximal normal* skin tolerance dose, when administered in a single treatment, is about 2,750 r. Thus, if field size is not considered there is practically no latitude of safe dosage, as Strandqvist indicates and shows in his graph of Figure 1. It can be seen that although he shows a range of safe dosage of 100 r for a single massive dose, or 300 r for a dose fractionated over a period of twenty days, there is actually overlapping of recurrences and complications even in this narrow zone.

A knowledge of the relationship between size of field and range of safe dosage in treating skin cancer is of real value in determining the required roentgen dose in treating skin cancer whether a massive or fractionated method is used. In an average group of cases, the safest dose that would result in the highest cure rate with the fewest complications would undoubtedly be the average between the maximum normal skin tolerance and the minimum curative dose for the particular size of field. However, it is necessary to individualize the treatment in certain patients according to the condition of the skin surrounding the lesion, the location of the lesion, and multiplicity of neighboring lesions. For example, a dose near the maximum normal skin tolerance could be safely given to a lesion on the face of a young, healthy patient where the lesion is surrounded by normal, healthy skin. However, if the patient is elderly with frail, dry, thin skin surrounding the lesion, a dose of similar magnitude would undoubtedly result in delayed healing if not late radiodermatitis or even necrosis. According to our experience, a dose just above the minimum curative level would give a good chance of cure without complications in such a patient.

Where the lesion occurs in skin with relatively poor collateral blood supply such as on the back of the hand, leg or on the back, even our minimum curative dose may be too much; *i.e.*, greater than the tolerance of surrounding skin. Our graphs are pertinent for face, neck and lip cancer only. We believe that most cancers on the back of the hand should be treated by plastic surgery. Some special consideration must also be given to skin cancers immediately overlying cartilage such as the ear and nose, not only in the selection of the quality of radiation to be used but in the total dose delivered and the method of fractionation. Doses a little lower than in other areas of the face and neck with increased fractionation should be considered. It is believed that these graphs will be of help to us in the future in selecting more correctly the proper dosage and method of administration, whether massive or fractionated, for each individual case and particular size of field. We hope that it may also be valuable as a guide to our colleagues in improving upon their results in the irradiation of skin cancer.

SUMMARY

1. In a review of the records and color photographs of 1,013 patients with cancer of the skin and a detailed study of 564 patients followed one year or more, there is evidence that the cumulative effect of fractionation, as determined from the graphical studies of the treatment factors used in our group of cases, supports the slope of Strandqvist's fractionation dose curve of roentgen therapy.

2. By segregating our cases according to the size of field treated, and plotting in the same manner as Strandqvist, the range of safe dosage is found to be very great for small fields and to diminish markedly as the size of the field increases. It contrasts widely from the small latitude shown by Strandqvist. In addition, it shows

that the minimum curative dose for a very small field is actually above that which the normal skin will tolerate when very large fields are used. A consideration of size of field is therefore of first importance in selecting the proper dosage and method of fractionation. It is essential for obtaining the highest rate of cure with the fewest recurrences and complications.

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THE DOSE-TIME RELATIONSHIP IN RADIOTHERAPY*

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THE science of photon dosimetry has now advanced to the point where it is possible to begin to think of dose (absorbed dose, by definition, International Commission on Radiological Units, 1953) in terms of absolute energy units. Is it not strange that the art of clinical dosimetry has not yet advanced to the point where it can be stated with certitude that a dose (whether cited as exposure in tissue roentgens or as absorbed dose in rads) of a predetermined magnitude given in a specified period of time is required to destroy a particular cancer?

That this, indeed, is the case can readily be determined by perusal of the literature dealing with reported case series of certain cancers, notably squamous cell carcinomas of certain sites. Such a perusal will show that there is not only a wide divergence of practice between different clinical investigators but there is, in some instances,

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TABLE I

Author	Series Squamous Cell Carcinoma of	Five Year Cures (per cent)	Average Tumor Dose (r)	Average Treatment Time (days)
Baclesse[2]	Hypopharynx	6	5,200–7,400	57–74
Binkley[3]	Larynx	31	5,400	27
Cutler[5]	Larynx	35	5,000	30
del Regato[7]	Lip	75	3,000–7,000	14
del Regato[8]	Skin (eyelid)	78	5,000	25
Desjardins and Figi[9]	Larynx	9	5,300	15–30
Eberhard[10]	Skin	83	3,600	14
Garland and Sisson[12]	Lip	80	4,000–6,000	28–35
Garland and Sisson[13,14]	Larynx	10	4,500–6,300	30–52
Garland and Sisson[12]	Tongue	17	5,500	28
Graham and Meyer[15]	Nasopharynx	15	5,000	40
Gynning[16]	Esophagus	5	6,500	35
Hale and Holmes[17]	Skin	95	2,750	1
			4,500	8
Harris, Silverstone, and Kramer[18]	Larynx and pharynx	55	4,000–6,000	28–40
Howes and Rosenstein[19]	Lip	96	4,000	1
			7,200	10
Ivey[20]	Lip	94	5,500	28
Jacobsson[21]	Hypopharynx		6,000	28
Köhler[22]	Esophagus		5,000	33
Leborge[23]	Larynx	27	5,000–6,500	21–58
Lenz[24]	Larynx	55	5,700–7,000	35–42
Martin and Martin[25]	Skin (ear)	50	3,800	12
Martin and Wright[26]	Skin and lip	40	4,400	4
Pack[27]	Esophagus		5,000	35
Parshall and Stenstrom[28]	Tonsil	26	2,600–4,400	21–30
Stetson and Schulz[32]	Eyelid	97	2,850	1
			3,600	3
Walker and Schulz[32]	Tonsil	15	6,000	24
Widmann[33]	Skin		3,000	6
Zuppinger[34]	Larynx and pharynx		5,000	20

a wide divergence in the doses administered to the individual cases of a given series. This is shown in the tabulation (Table 1) of some reported case series. (Carcinoma of the uterine cervix is not included because the dose gradients usual in the treatment of this disease are such as to make the computation of tumor dose rather arbitrary.) Dose is expressed in units of tissue roentgens of exposure and this connotation of the term is used throughout this presentation. This tabulation gives average doses as derived by us from the case series summarized. If another were to summarize the same material, slightly different average doses might be derived or different dose units might be employed. Such variations in interpretation would not, however, affect the relative differences between the various series.

This wide divergence of practice may be shown graphically by indicating the average doses and average treatment times as points on a scatter diagram relating dose and time (Fig. 1). Such wide divergences as demonstrated here may be given any one of the following interpretations:

(1) That the dose, *per se*, is not critical and that success or failure depends upon other influences as yet undetermined. Another way of stating this is that very great differences in doses are equally successful.

(2) That the critical, or optimal, limits of dose have not yet been or cannot be determined, or

(3) That within these diverse series may be found some observations more critical than others and that from such more critical observations valid conclusions may be reached.

In any event, the material summarized is fairly representative of the status of clinical radiation dosage as reported. On the other hand, it may not be representative of the thinking of contemporary practitioners of clinical radiation therapy. It is probable that interpretations numbered "1" and "2," above, would be discarded by most and that a search would be made for critical observations of dose-time relationships. Still, it is not unusual to hear the statement made: "I don't know how much of a dose to give; I just have to follow the patient along and decide when he's had enough." This, without meaning to deprecate the value of sound clinical judgment in radiation therapy as in everything else clinical, is somewhat vague, especially, as the observable effects upon which one would like to base a conclusion only follow by an interval of time the administered dose. It becomes desirable, then, to search for very critical and significant observations in the mass of clinical data presented in the literature.

If a dose-time relationship for the cure

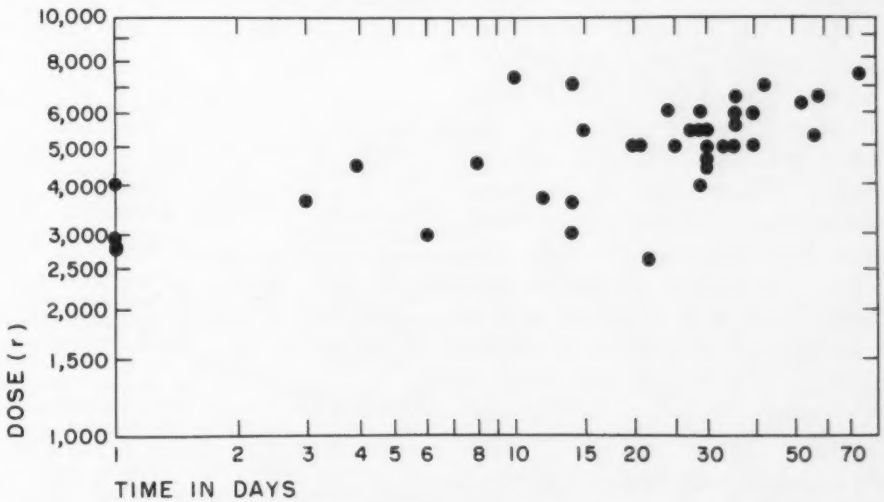

Fig. 1. Scatter diagram of data in Table 1 relating dose and time.

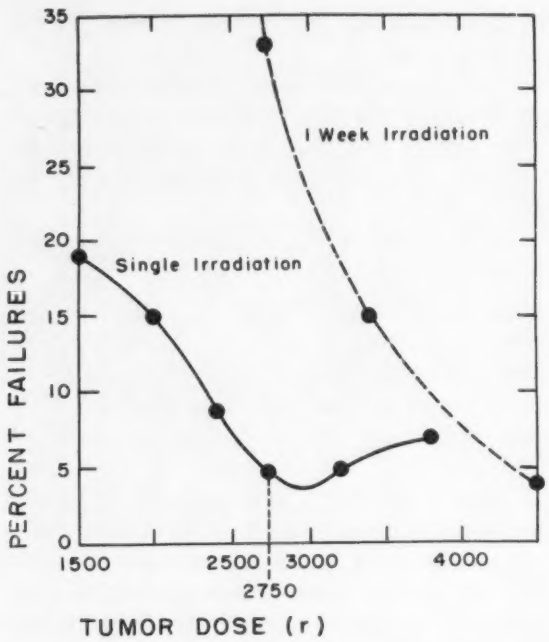

FIG. 2. Minimal (optimal) doses for single and one week irradiations (Hale and Holmes[17]).

(or, better, regression, as it will be stated hereafter) of squamous cell carcinoma is to be established there must be, of course, a point of origin,—the minimal dose which will result in the destruction of squamous cell carcinoma when administered in a single sitting. This dose can be stated with considerable accuracy to be 2,700 tissue roentgens of exposure (about 0.5 mm. Cu half-value layer). This has been established by Hale and Holmes[17] from their series of 893 squamous and basal cell carcinomas of the skin. Figure 2 is adopted from their presentation and it shows the percentages of failures as related to dose for both a single irradiation and for fractionation extending over a period of one week. At the single dose level of 2,750 r the cure rate is 95 per cent and at a higher dose it becomes less. There is no evidence to support any belief that modification of this dose for a single irradiation will result in a greater cure rate. This, then, is the minimal cancerocidal dose for a single irradiation. As such, it becomes the point of origin for the plotting of the dose-time relationship for the regression of squamous cell carcinoma.*

Hale and Holmes also provide critical data for a one week irradiation period. The optimal dose for this period is 4,500 tissue roentgens of exposure and the cure rate with this dose is 96 per cent (Fig. 2). This establishes another point for the plotting of the dose-time relationship.

One of the most critical analyses of the results of treatment of an internal cancer to be found in the literature is that of Jacobsson[21] in his report of 322 cases of carcinoma of the hypopharynx from Radiumhemmet. The optimal results were obtained with a tumor dose of 6,000 tissue roentgens of exposure in twenty-eight days. A permanent cure was obtained with a lower dose in only 2 cases. Doses of 6,600 r or more resulted in fatal complications in all cases.

These three diverse but very critically determined points in the dose-time relationship are plotted in Figure 3 on a double logarithmic system of coordinates.† It is evident that they fall on a straight line. Is this simply a matter of chance or of selection or is there other evidence to support the thesis of an optimal relationship between dose and time for any given effect? There is, of course, the evidence of Strandqvist's[31] most original investigation and the regression line developed by him is shown as line "A"‡ of Figure 4. Garcia,[11] in a most exhaustive and illuminating re-

* In plotting the dose-time relationship an irradiation series is construed as a series of events occurring within a given period of time, but, considered individually; the events themselves have no time significance for as such they can have no interval or over-all time. A single irradiation is, therefore, a single event without time significance. If the dose is complete in a single sitting the series ends with that. If it is not, then the first irradiation is simply the first event in a series of events. Strandqvist,[31] in order to "smooth" his plot, gave to the single, or first, irradiation a finite time of less than unity on the time coordinate.

† The double logarithmic system of coordinates is used because the work of Strandqvist suggested that a parabolic relationship existed between dose and time for a given effect. Studies of Cohen (4), Paterson (29), Garcia (11), Andrews and Coppedge (1), and others have tended to confirm this relationship. The equation of the parabola becomes a straight line in a double logarithmic graphical representation. See footnote, page 593.

‡ The regression line, "A," as drawn is somewhat modified from that of Strandqvist. As modified, a single irradiation is represented as $t = 1$. Strandqvist represented it as $t < 1$.

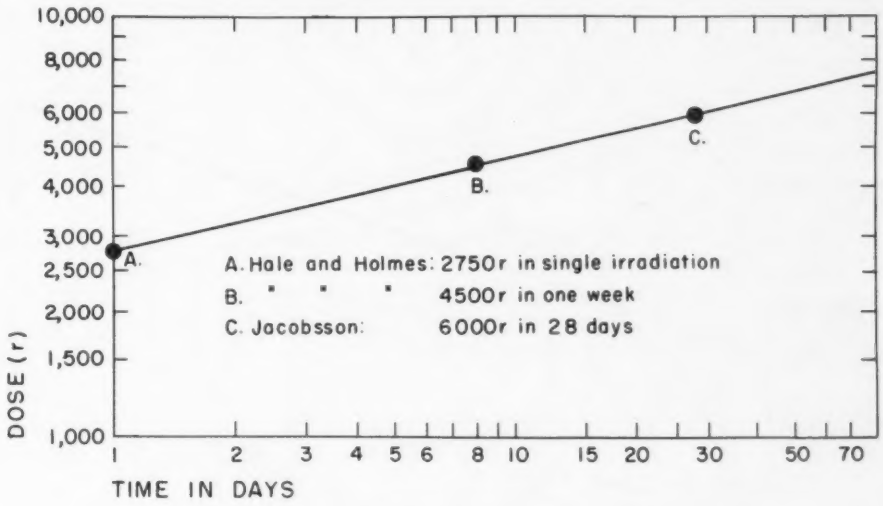

FIG. 3. Plot of the data of Hale and Holmes[17] and of Jacobsson.[21]

cent study, has developed a regression line for carcinoma of the uterine cervix and this is shown as line "C" of Figure 4. The regression line developed here from the data of Hale and Holmes and of Jacobsson is shown as line "B" of the same figure. Finally, several points developed by Paterson[29] are also shown. Supporting evidence for the concept of an optimal relationship between dose and time for a given effect was also advanced by the senior author (J.R.A.) in a previous study where such a relationship was shown for the moist desquamative reaction of the skin from data developed by three British investigators (Ellis, Jolles and Mitchell, and Paterson. See Andrews and Coppedge).[1] This relationship between dose and time for the moist desquamative reaction of the skin is shown in Figure 5. It seems, therefore, reasonable to conclude that there is a fixed or optimal relationship between dose and time for a given effect and that this relationship can be represented by a straight line on a double logarithmic system of coordinates.*

* Such a plot has the general equation of the parabola, $y = kx^n$, where n is a positive number. When logarithms of both sides of the equation are taken it

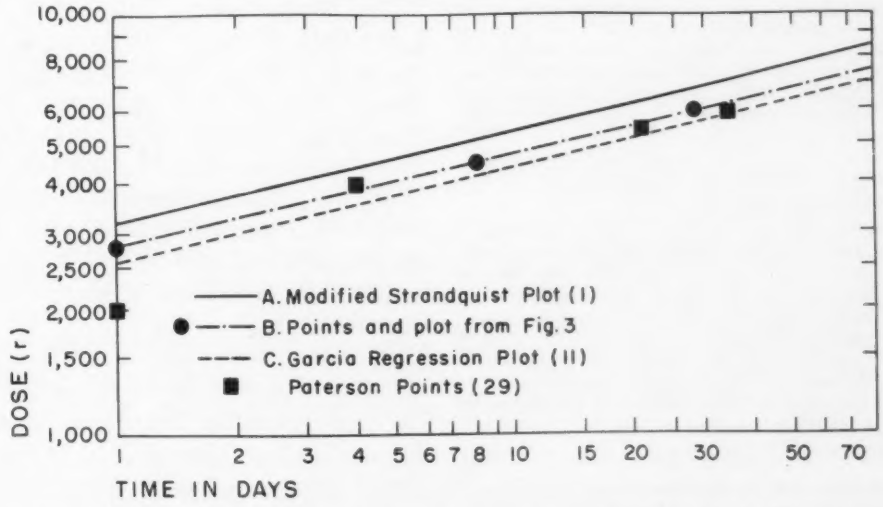

FIG. 4. Plots as developed from Strandqvist (Andrews and Coppedge[1]), Figure 3 (this text), Garcia[11] and Paterson.[29]

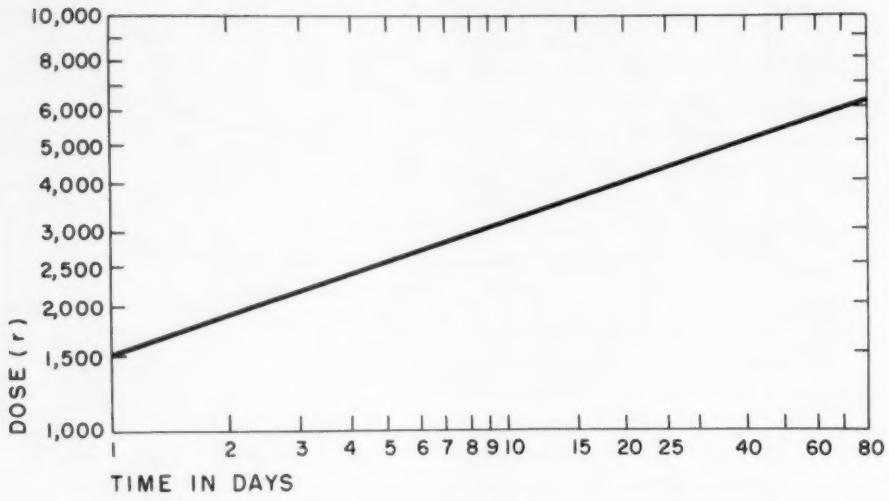

FIG. 5. The dose-time relationship for the moist desquamative reaction of the skin (Andrews and Coppedge[1]).

There are certain implications inherent in the development of a concept of this sort. One such is that treatment time, *per se*, is no longer important unless response is modified by other factors which are as yet unknown. (See "Addendum.") Another, and perhaps the most important implication, is that it cannot and probably will not be shown that therapeutic results are improved by any significant deviation from the values shown by the regression line of Figure 3. It follows from this that current therapeutic efforts should be directed towards attaining the dose levels indicated by the dose-time relationship provided only that the radiation tolerance of adjacent tissues will support such dose levels. (As an example of this limitation Garcia has shown in the study previously cited that certain pelvic tissues in the female may not support such dose levels, at least with the distribution of dose commonly employed.) Finally, it is to be implied that there are limits of accuracy in the derivation of any such relationship and that it is reasonable to expect that there is a range of doses which may be equally effective. It is not to be expected, however, that this range of doses of equal effectiveness will be greater than plus or minus 20 per cent and it is probable that such an upper limit represents a generally necrotizing dose.

In conclusion, the dose-time relationship for the regression of squamous cell carcinoma can be developed as shown in Figure 6 where the optimal regression line (from Fig. 3) is shown together with lines defining the limits of the plus and minus 20 per cent variations from the values of

becomes,

$$\log y = \log k + n \log x.$$

If values of $\log y$ are plotted as ordinates and values of $\log x$ are plotted as abscissas, a straight line results because n and $\log k$ are both constants. Instead of plotting the logarithms themselves the appropriate values of y and x may be plotted on a double logarithmic system of coordinates, such as used in this and other studies of the dose-time relationship, and a similar straight line results. Such a plot is useful in determining the constants of a parabolic equation for the slope (ratio of vertical to horizontal increase) of the line and its point of interception on the ordinate give, respectively, n and k.

The equation,

$$y = kx^n$$

may be rewritten as,

$$D = kt^n$$

where D is the total dose in t days required for a specific radiation effect, k is the dose constant for the specific effect when the dose is given as a single irradiation (2,750 r for the regression of squamous cell carcinoma), t is the treatment time in days, and n is an exponent derived from the slope of the regression line (0.23 as plotted in Fig. 3). If, then, the regression of squamous cell carcinoma is the specific effect required the equation may be completed for this effect by the substitution of the appropriate values of k and n. The equation then becomes,

$$D = 2{,}750t^{0.23}.$$

The dose (D) for any treatment time (t days) may then be found. Appropriate substitutions may, of course, be made for the expression of the dose in rads and such substitutions will not modify the general relationships expressed by the equation.

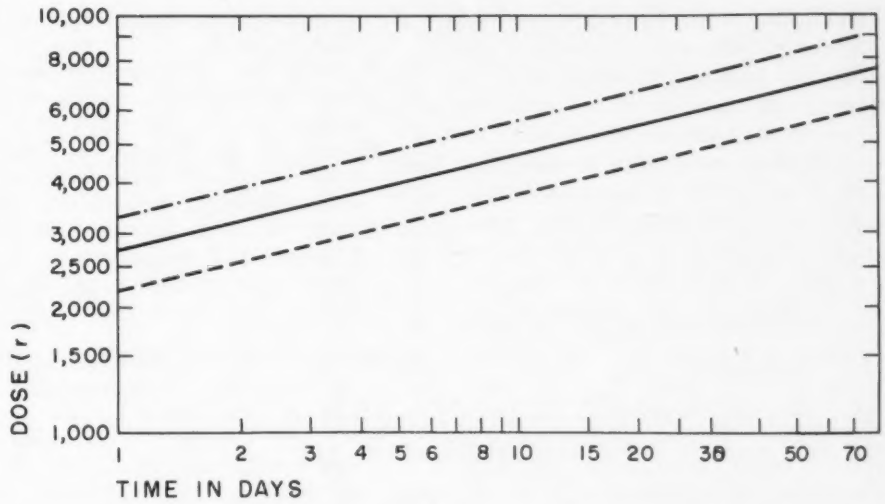

FIG. 6. The optimal dose-time relationship for the destruction of squamous cell carcinoma together with the plus — · — and minus — — — 20 per cent deviations from the optimal regression line.

the regression line. It seems highly improbable that clinical results in the treatment of squamous cell carcinoma will be improved by departure from the values shown.

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ADDENDUM

One might speculate here as to the possible effect of very great prolongation of the treatment time to, say, seventy-five or more days, assuming that the plots for the regression of squamous cell carcinoma and the moist desquamative reaction of the skin are continuous, with the same slopes, to infinity. In the plot of the dose-time relationship for the moist desquamative reaction of the skin n is found to be 0.32 while n is 0.23 for the regression of squamous cell carcinoma. This may mean one of several things: that the radiation, when appropriate doses are considered, is relatively more effective in causing regression of carcinoma than in inducing the skin reaction or, conversely, that the recovery factor for the skin reaction is greater than that for carcinoma; that the differences are inherent in the responses which are of different degree; or it may mean, simply, that the observations are in error. Let us assume that it means that the recovery factor for the moist desquamative reaction of the skin is greater than the recovery factor for the regression of squamous cell carcinoma. This would be in line with the oft-repeated clinical observations of apparently better results with prolongation of the treatment series. The two plots may be related by a so-called "safety factor" (f_s) which establishes a ratio between the two plots, or responses, for any given time, as,

$$f_s = \frac{\text{cancer dose in } t_1}{\text{skin dose in } t_1} \times \frac{\text{skin dose in } t_x}{\text{cancer dose in } t_x}.$$

Substituting the appropriate values for the skin and cancer doses for t_1 (t = 1), the equation becomes,

$$f_s = \frac{2750}{1500} \times \frac{\text{skin dose in } t_x}{\text{cancer dose in } t_x}.$$

At $t_x = 1$ the ratio, f_s, is, of course, unity. For this and other values of t the ratios are as follows:

Duration of Treatment Series Time (t_x) in days	f_s
1	1.0
5	1.2
10	1.25
30	1.35
50	1.45
75	1.5
100	1.55

If what has been developed here has any foundation in fact, it becomes apparent that gross differences would hardly be observable short of about thirty days. This may have something to do (aside from the daily tolerance of

patients under treatment) with the widespread but empirical use of such a period of time for the accomplishment of a treatment series. More or less significantly greater differences would be observed from seventy-five to one hundred or more days. It is, then, interesting to speculate as to what the clinical effect on cancer would be if a treatment series were extended over a period of, say, seventy-five to one hundred days with doses as indicated by extension of the regression line for squamous cell carcinoma.

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TIME-DOSE RELATIONSHIPS*

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IT WAS recognized very early in the history of radiation therapy that the effect of a dose of radiation varied according to the time in which it was delivered. Regaud and Ferroux[29,30] showed that this variation is not the same for all tissues when they found that although it was impossible to give a sterilizing dose to rabbit testes in a single treatment without ulceration and necrosis of adjacent tissues, this result could be accomplished if the dose were broken into four fractions. Then the effect on the skin became very much less while the effect on the testicle was at least as great. Coutard[6] applied this finding to the treatment of epitheliomas of the tonsillar regions, hypopharynx, and larynx, and found the results of long treatment time superior to short, as evidenced by a greater differential effect on tumor and normal tissues. Largely as a result of his report, the usual therapy technique became daily treatment over a period of weeks. It is proposed in this paper to analyze what is known of the effect of time on response to dose in order to arrive at more exact ideas of time-dose relationships and perhaps find indications for better distribution of radiation in time which would improve clinical results.

Dose may be varied in time in three ways: the intensity, or r/min. at which it is delivered, the over-all time from the beginning of the first treatment to the end of the last, and the degree of fractionation, or time interval between treatments.

Coutard believed that it was an essential part of his technique to deliver the radiation at a very low intensity, about 2 r/min. at the tumor. However, in the course of years a clinical impression was built up that this was not necessary. McWhirter[19] demonstrated this in a clinical experiment. He gave treatments twenty-four hours apart for a total time of one week, and found that for three dose effects —erythema, cure of rodent ulcer, and lethal dose for skin epithelioma—there was no difference with intensities from 12 r/hr. to 1,273 r/hr. for the same total dose. Another study,[33] using 12 fractions and doses for erythema and 20 per cent above and below this dose, showed no difference for intensities of 5.25 r/min. and 112 r/min. It would seem, then, that for the usual therapy technique of daily irradiation over a period of time, there is no evidence that the result is dependent on the r/min. with which each treatment is given.

The effect of extending the over-all time has been studied systematically by many investigators. In one group of experiments the same total dose was given in a single exposure, using different intensities, so that the over-all time varied. Some dose responses studied in this way are lethal effect on bean roots,[12] number of cells in mitosis in tissue cultures,[3] percentage death of chick embryos,[17] LD_{50} for mice,[35] and human skin erythema.[22] In all these experiments the effect of the dose remained the same as the time was extended until a critical time was reached, after which the effect diminished. This critical time differed for different cell types, and Pack and Quimby have suggested that it may be related to the life span of the cell. The generally accepted explanation for this is that after a certain latent time recovery of the cells from the effects of radiation becomes apparent. The time-dose curve must be horizontal during the latent period and only begin to rise after the critical time is passed. The length of the latent period is not known with any exactness for most clinical situations, with the single excep-

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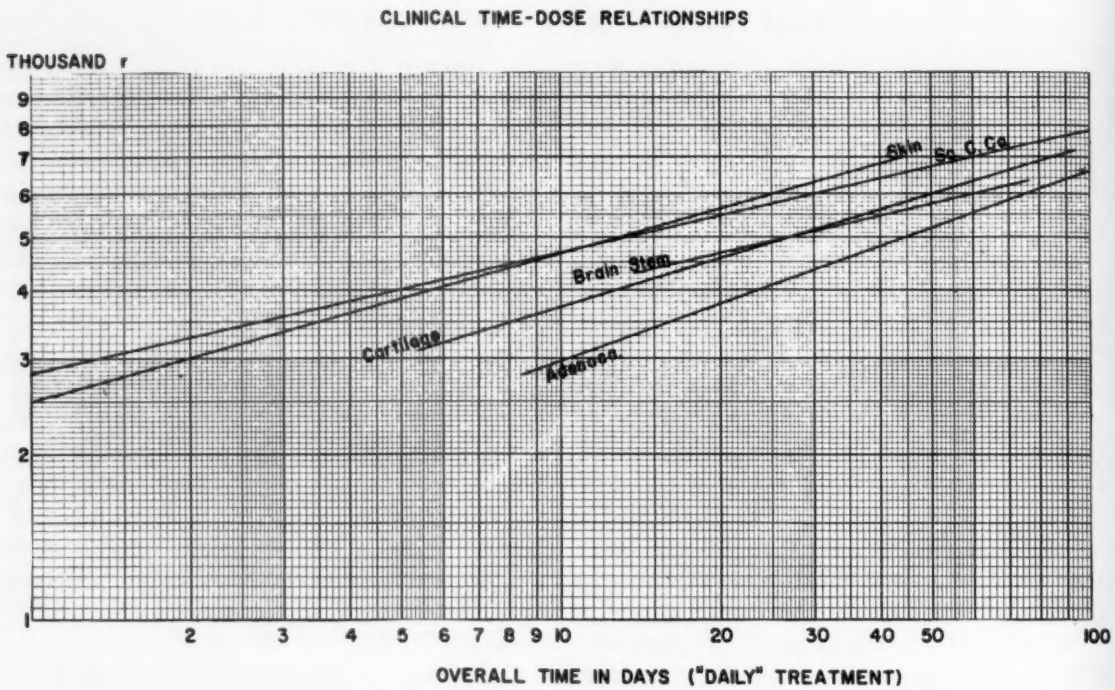

FIG. 1. *Skin*—tolerance (4×6 cm.) from Figure 2. *Squamous cell carcinoma*—cure of skin cancer (5–30 sq. cm.) Strandqvist.[34] *Brainstem*—tolerance (5–7.5 cm. diameter) Boden.[2] *Cartilage*—tolerance (12–40 sq. cm.). Fitted to data of Baclesse and Gunderson.[1] *Adenocarcinoma*—minimal cancerocidal dose at Point *C* for corpus uteri, Costolow, Nolan, Budenz and Du Sault.[5] "Daily" treatment means treatment five or six days a week and, in order to arrive at over-all time, the day on which the first treatment is given is called *O*.

tion already mentioned of skin erythema, where the work of several observers seems to indicate that it is about four hours. Treatment given in a single massive dose usually occupies only a small part of the latent period, and if this dose is plotted against over-all time it will, in general, not lie on the straight line drawn on log-log paper, which is usually used to demonstrate time-dose relationships, following the suggestion of Strandqvist.

This line represents the equation, $D_2/D_1 = K(T_2/T_1)^n$, where D_2 and D_1 are the doses corresponding to the over-all times, T_2 and T_1, K is a constant related to radiosensitivity, and n is the slope of the line and is related to the rate of recovery. Most clinical data seem to fit this line reasonably well. Some examples of time-dose relationships of this sort taken from the literature or fitted to published data are shown in Figure 1. No attempt should be made to draw conclusions about relative radiosensitivity from these curves, as each curve represents some definite percentage on the sigmoid dose response curve, and this is not the same percentage for all the curves shown. In addition, the areas represented vary according to the region treated, and the size of the area affects the absolute value of the dose. It does not, however, affect the slope of the time-dose line, provided the dose effect is the same, as is shown (Fig. 2) for normal tissues by skin tolerance doses for different sized fields and for malignancy (Fig. 3) by two curves fitted to data on carcinoma of the larynx where the fields were of different sizes because of the stage of the disease.

An understanding of the factors affecting the slopes of the time-dose curves should lead to suggestions for improving the differential effect between tumor and normal tissue. If the curves are re-plotted

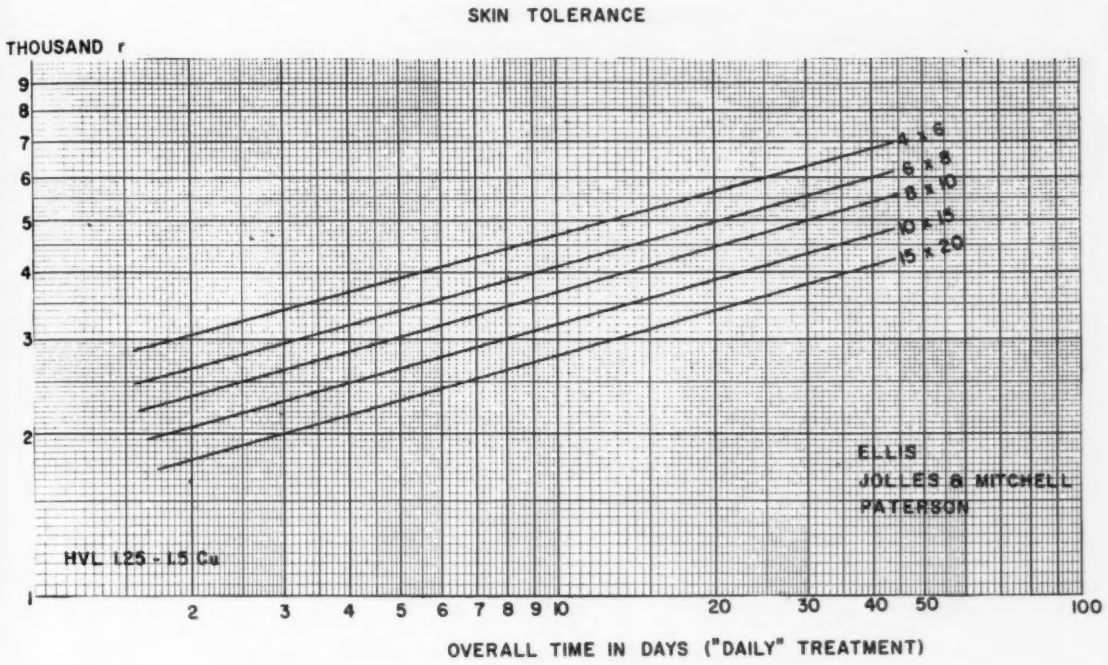

Fig. 2

from a common point, it is easier to compare slopes. In Figure 4 this has been done, using one day for this point. There is no significance to the time of one day, any time might have been used as well to demonstrate relative recovery rates. The value of n shown for squamous cell carcinoma is that of Strandqvist,[34] 0.22. His

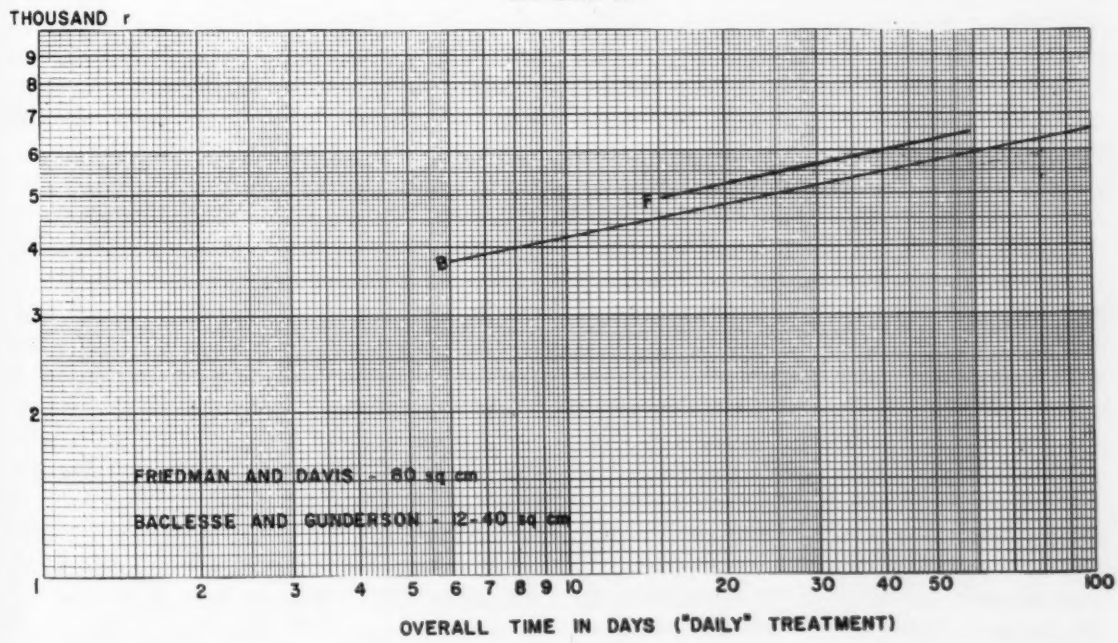

Fig. 3

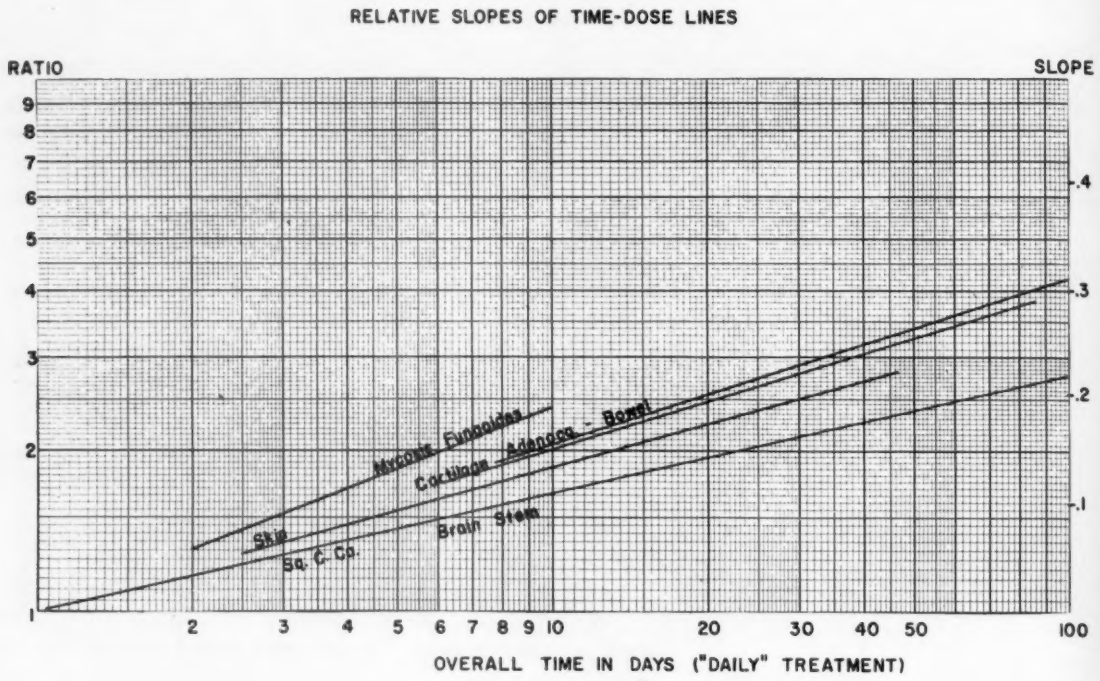

Fig. 4

data refer to skin lesions, but similar data for squamous cell carcinoma of the cervix[11,21] and of the larynx[1,9] fit fairly well, slopes ranging from 0.20 to 0.23. It is possible that variations are due to location of the tumor, that is, to tumor bed, but this cannot be demonstrated, and they may be merely the usual variations found in clinical material. Recovery exponents for human skin have been quoted in the literature all the way from 0.22 to 0.33. That shown here is 0.27. Some writers have included different degrees of skin injury, ranging from threshold erythema to necrosis, in the data used for determining the slope, but since, as will be shown later, recovery rate depends on the degree of injury, it seemed best to limit the data used to a clearly defined "tolerance" reaction. The work of Ellis,[7] Jolles and Mitchell,[13] and Paterson[26] was used for this curve, and a least squares line fitted to each set of data to arrive at this slope. The slope for adenocarcinoma is based on curves published for breast[4] and corpus uteri[5] which show good agreement. The curves for bowel,[20] cartilage,[1] mycosis fungoides,[10] and brain stem, cervical cord, and cerebrum[2] are based on single reports and need substantiation before being accepted. They are presented here as tentative only.

From these curves it is at once apparent that cell type is one factor of importance in determining time-dose relationships. They also explain the advantage of extending the over-all time in the treatment of squamous cell carcinoma if skin, bowel, or cartilage lies in the treatment field, since the dose causing damage of these normal tissues increases with time more rapidly than the lethal dose for the tumor. It should be remembered that a dose high enough for a cancerocidal effect in most patients will also be above normal tissue tolerance for some patients, unless the respective doses are widely separated. Since extension of over-all time gives greater separation, there will be fewer patients in the region of overlap of the two effects. This advantage does not hold, however, for adenocarcinoma, at least of the breast or uterus. Indeed, there seems to be actual disadvantage to prolongation of treatment time when skin is the critical tissue for over-

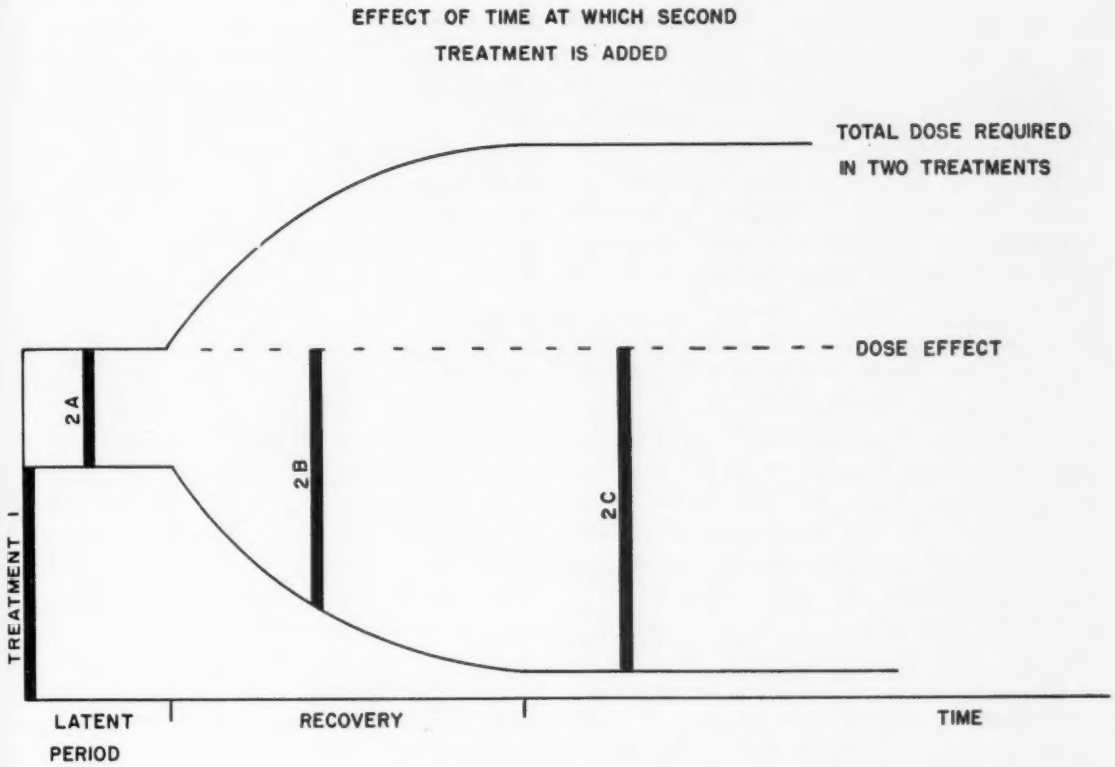

FIG. 5

dosage, since the line for adenocarcinoma rises more rapidly than that for skin. How, then, can the differential effect for these adenocarcinomas be increased? If means could be found for lessening the slope for cancerocidal effect and/or increasing that for normal tissue tolerance, then extension of the over-all time would give greater separation of the respective doses, and hence, less overlap of the two effects.

The third way of varying dose in time, namely, degree of fractionation, will be examined next for a possible answer. The influence of the time at which a second treatment is given, following an initial treatment, is illustrated by the curves shown in Figure 5. If the second dose (*2A*) is given during the latent period, the effect will be simply that of the sum of the two doses and the total dose necessary for the effect will be the same whether given in a single short treatment, continuous irradiation throughout the latent period, or any type of fractionation within the period. If it is given after recovery begins (*2B*), its result will depend on how much of the first dose remains effective, and this is a function of the over-all time, the effective amount becoming less as the over-all time increases. Conversely, to produce a given effect, the dose which must be added by the second treatment, if given during recovery, becomes increasingly larger as the time increases, and the total dose to be given in the two treatments also increases at a rate which can be shown by a straight line drawn on double log paper, such as that already mentioned. The total dose required will depend only on the over-all time, and variations of timing within the recovery period will not change the time-dose curve. This can be illustrated numerically for skin erythema as follows: If the first treatment consists of 300 r, then a second treatment (*2A*) given at any time up to four hours would need to be 225 r, or a total dose of 525 r, to produce an erythema; if it were added any time after four hours

(2*B*) the amount required depends on the over-all time, being 340 r for a six hour interval, 400 r for twelve hours, etc., or total doses of 640 r, 700 r, etc., and this dependence holds at least up to ninety-six hours. After a certain length of time recovery ceases, and a second dose (2*C*) added at any time after this will have the same effect regardless of the time at which it is given, and the dose required for a given effect will be the same. A straight line joining these two doses will have a lower and lower slope as the time interval between them increases. For timing of this type the time-dose curve changes with the interval between treatments and this would have to be specified. This discussion of timing with respect to recovery applies to any two successive treatments, and when a series of equal treatments is given, as is usual in therapy, both types of timing may occur in the same series. The longer the over-all time used, the smaller each individual dose becomes, and eventually this dose might be small enough so that recovery from the first dose would be essentially complete before the following dose is given, but as repeated doses are given, since the recovery is not 100 per cent, the cumulative dose effect becomes large enough so that the recovery phase would extend into the following treatment period. The net result for very long over-all times would be some lowering of the total dose required. This means that the straight line relationship between the logarithms of dose and time cannot be expected to continue indefinitely, and the complete time-dose curve may be somewhat sigmoid in shape. A clue to optimum over-all time may lie here. Experimental evidence of this was not found in the literature, and clinical dosage data show so much variation that it cannot be shown in this way. However, the last values in the skin tolerance curves do show some slight tendency to fall below the curve given, and the erythema data show some hint of the sigmoid shape. In each case, however, the points are too few to justify conclusions of this sort, and for the present the statement must remain theoretical. Nevertheless, for this reason the time-dose curves should not be extrapolated beyond the clinical data on which they are based.

The significance of the recovery cycle with respect to time-dose relationships like those shown here is that if recovery begins sooner and/or proceeds more rapidly in normal than in tumor tissue, then treatments timed so that each falls into the period of recovery from the preceding one (or ones) will result in a lower slope for the cancerocidal time-dose line than for the normal tissue tolerance line, and consequent advantage to extension of over-all time. This may be the case for squamous cell carcinoma and skin. Tissues with identical recovery but different radiosensitivity would have parallel time-dose lines for any type of fractionation, and no treatment time would have any advantage over another as far as differential effect is concerned. Finally, if the tumor recovers faster than the normal tissue, treatment during recovery will make extension of over-all time a disadvantage. The discussion above suggests the possibility of altering this situation by timing the treatments according to the relative recovery periods of tumor and normal tissue. The slope of the cancerocidal curve might be lowered by extending the time interval between treatments beyond the recovery period. If this timing still brought the treatments within the recovery phase of the normal tissue, its time-dose curve would not be changed, and it might be possible to obtain a lower slope for the tumor than the normal tissue. Knowledge of the length of the recovery phase is, therefore, of great importance.

Recovery of the skin has been studied carefully by Kepp and Seyfarth.[15] They pointed out the latent period before recovery is apparent, and showed that recovery is delayed and prolonged by larger doses, whether given in one massive dose or as an accumulation of dose effect from a series of small fractionated treatments. They felt that recovery from very small doses was complete in twelve hours, but

that with larger doses recovery was still going on after more than twenty-four hours. They also showed that extending the time past eight days produced a "renewed sensitivity," as they described it. The work of Quimby and MacComb[18,27] on the dose required to produce an erythema was mentioned above. They also pointed out that a total dose given in five daily treatments or in two treatments ninety-six hours apart gave the same effect, and another, comparing twelve daily treatments with treatment on the first, fifth, eighth and twelfth day, again gave the same result, or that the effect depended on the over-all time. In other words, under these conditions the treatments were falling into the recovery phase. It seems probable that for the larger doses used in therapy in approaching skin tolerance, since the recovery rate would be slower, this degree of fractionation would still bring each successive treatment into the recovery phase of the preceding, and that fractionation with time intervals up to four days would not change the total dose required in a given time, or would not change the time-dose curve shown above for skin tolerance, at least within this over-all time.

The same thing does not seem to be true for all tissues. Sambrook and co-workers,[31] comparing 500 r twice a week with 200 r five times a week, found the former gave better results in breast carcinoma and the latter in squamous and basal cell carcinoma of the skin. Koller and Smithers,[16] spacing their treatments according to the rate of recovery of the tumor cells as determined by cytological examination during treatment, were able to obtain good results with much smaller doses than those required with daily treatment. This work all seems to indicate that for some tumors, at least, better results might be obtained by using longer time intervals between treatments than twenty-four hours. This was mentioned by Cohen as a possible solution to the problem of adenocarcinoma of the breast.

Information on the effect of fractionation is also available from animal experiments. That the time-dose relationship may be changed by the interval between treatments is shown by data for LD_{50} for mice obtained by Paterson and co-workers,[24] comparing daily treatment with radiation given in two fractions, the latter technique requiring less radiation (Fig. 6). Paterson and Thompson,[25] working with chick fibroblasts grown *in vitro*, gave three types of treatment: continuous, fractionated at two hour intervals, and two fractions, the over-all time in all cases being forty-three to fifty-three hours, and found the percentage survival the same for the first two techniques, but the third gave greater effect. An earlier work[23] extending the over-all time to twenty-one days and fractions to daily increased the effect further. Regaud's impression that fractionated radiation had greater effect on rabbit's testicles than a single dose has been confirmed by others.[8,32] An explanation given by Paterson for the increased effect with fractionation is that some cells are in a brief radioresistant phase during one treatment and are relatively unaffected, but may be acted upon by the next treatment. There is also some evidence for a critical degree of fractionation, that the effect is first increased and then decreased as the time interval between treatments is lengthened. For example, there was more corneal damage in rabbits with

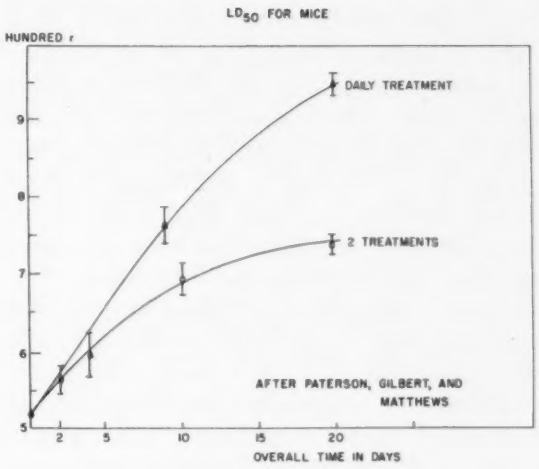

Fig. 6

treatments given three days apart than with a single massive dose or an interval of more than three days.[28] For the same total dose, lymphoma incidence in mice was the same for a single exposure or for daily exposures up to eight days; there was a striking increase when intervals of from four to eight days between treatments were used, but when the interval was increased to sixteen days the response was back to that of daily treatments.[14] Lower and lower slopes for the time-dose curve, then, cannot be obtained by extending the interval between treatments indefinitely.

It is obvious from all these experiments that the problem of time-dose relationships, and particularly of the effect of fractionation, is an extremely complicated one. The discussion of the effect of timing of treatments with respect to the recovery cycle explains only one aspect of it. Variations of radiosensitivity in different periods during the life cycle of the cell affect dose response and may reinforce or lessen the effect of the recovery cycle. Interaction among the various factors may account for the periodicity of radiation effects which has been discussed by many authors, and for the critical fractionation periods mentioned here. It is known that the response of cells to radiation can be altered by such means as chemicals, temperature, hormones, etc., and it is possible that they may also alter the time-dose relationship, and that the change may not be the same for all tissues, particularly that it may be different for tumor and normal tissues. There is a very great deal yet to be learned about methods of influencing time-dose relationships, but the evidence so far obtained is sufficiently encouraging as to the possibility of improving treatment techniques by this means to justify spending time on the problem.

SUMMARY

After radiation treatment is begun there is a latent period varying in length for different tissues and different reactions, during which there is no change in dose required for a given effect and the time-dose line is horizontal. Treatment given in a single dose should not be plotted on the type of time-dose graph shown here, unless the dose line is drawn horizontally through this point, and no attempt is made to fit it to the line through other dose values. Next a recovery period is evident, whose length again is dependent on the size of the dose and type of tissue, during which the dose required is dependent on the over-all time, and the time-dose relationship is represented by a straight line, plotted on double log paper with a slope related to the recovery rate. For continuous irradiation or fractionation with a small time interval between treatments this relationship holds over a long period of time. If the treatments are more widely separated in time, they may fall into a period during which no recovery is going on. In this case the dose required is independent of the time at which each treatment is given, and the slope of the time-dose curve becomes less as the time interval is extended. On the other hand, other factors such as variation in radiosensitivity at different periods in the life cycle of the cell may operate to increase or decrease dose effect at certain times. Therefore, a statement of dose given should include both over-all time and degree of fractionation, since otherwise the dose cannot be counted on to produce a certain effect. Time-dose lines should not be extrapolated beyond the time limits of the data on which they are based, either to shorter times to find the dose for a single treatment since, in general, this will not lie on the curve, or to longer times, since there is no evidence that the relationship holds indefinitely, and there is theoretical reason to think that it will not. There is sufficient evidence that proper timing of treatments can increase the differential effect of irradiation to warrant further study of this problem.

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DISCUSSION

EDITH H. QUIMBY, New York, New York. Miss Du Sault leaves very little for me to say. I suspect that right now she knows more about time-dose relationships than anyone else in this country,—or maybe anywhere. She has been interested in the subject for a long time. Her published paper contains a list of 35 references, and this, she tells me, has been selected from a much larger group.

Experimental studies on various biological organisms and on the human skin are informative, but none of them gives a direct idea of the behavior of other human tissues, normal and abnormal. Pertinent information on time-dose relationships in clinical radiology can only be amassed by careful observation of patients under and following treatment, and critical analysis of their dosage data. Contributions of this sort are few. Everyone knows about the work of Strandqvist, but fewer are aware of that of Paterson, Garcia, Ellis, and others. The collection and correlation of information here presented is going to be very valuable.

Empirically, some radiologists vary their time-dose plans for different types of lesion, and possibly for different qualities of radiation. Others find a pretty good average adjustment factor and stick to it. One of the important things brought out in this paper is the variation in slope of the time-dose curve from 0.2 for squamous carcinoma, to 0.3 for adenocarcinoma of the bowel, and to 0.4 for mycosis fungoides, both of the latter two being steeper than that for skin. This demonstrates the need for development of different time factors for different diseases. It appears that prolongation of treatment time with an adenocarcinoma might be a real disadvantage from the point of view of the slower recovery for skin.

The choice of interval also appears to be more significant than we have realized. Daily or twice daily treatments may not be at all the best in all lesions. Certainly it would be more convenient to treat twice a week rather than five times, and if results were as good or better, it would be a great help.

We keep trying to improve our radiation therapy by improving physical factors, such as increasing kilovoltage. Perhaps we should pay more attention to biological factors such as those discussed in this paper. Obviously we need much more information along these lines, and I hope this report will stimulate investigation.

I am sure we are all grateful to Miss Du Sault for bringing us this very complete analysis of the present status of the matter.

VOL. 75, NO. 3

TESTING FOR SIGNIFICANT DIFFERENCES BETWEEN RESULTS OF VARYING TREATMENT TECHNIQUES

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IN THE treatment of cancer the advent of cobalt 60 beam therapy and the availability of supervoltage therapy units have led to a consideration of the problem of assessment of various forms of treatment. The purpose of this paper is to discuss the question of the sensitivity of Student's *t*-test in testing for a significant difference between the results of two methods of treatment. It is customary to use the test without taking into consideration the number of cases in each series which (1) would have lived without treatment, and (2) would have died regardless of the type of treatment received.

The ideal situation would be one where these cases are identifiable and excluded from the series. In practice, however, this is usually not possible. The question arises then, does Student's *t*-test in such a case lead to a claim of significant difference between two results when none exists?

The discussion which follows indicates that, for all values which are practically possible for the number of cases in (1) and (2) above, the sensitivity of the *t*-test decreases, with the result that the test might lead to a conclusion of "no significant difference" when a significant difference actually exists. It will be appreciated that the indication of a significant difference where none exists will never occur. The error in the use of the test, then, is a conservative one.

Consider two series of patients as follows:

(a) Series A consisting of N patients receiving Treatment I with S_1 patients surviving five years.

(b) Series B consisting of N patients receiving Treatment II with S_2 patients surviving five years.

Suppose that in each of the two series there are x individuals who would have survived for five years without treatment and y individuals who would have died irrespective of the type of treatment received. Since in any comparison of results one must begin with closely comparable series, it is logical to ask that x and y be the same in each of the two series (but not necessarily equal to each other).

If t is calculated in the usual manner, which is equivalent to assuming $x=y=0$, it follows that

$$t=t_1=\frac{\left|\frac{S_1}{N}-\frac{S_2}{N}\right|}{\sqrt{\frac{S_1(N-S_1)}{N^3}+\frac{S_2(N-S_2)}{N^3}}}$$

On the other hand, if the individuals in (1) and (2) (as signified by x and y) are considered it follows that

$$t=t_2=\frac{\left|\frac{S_1-x}{N-x-y}-\frac{S_2-x}{N-x-y}\right|}{\sqrt{\frac{(S_1-x)(N-S_1-y)}{(N-x-y)^3}+\frac{(S_2-x)(N-S_2-y)}{(N-x-y)^3}}}$$

The comparison of the relative magnitudes of t_1 and t_2 is made by considering the ratio

$$\frac{t_1^2}{t_2^2}\gtreqless 1, \text{ or } t_1^2-t_2^2\gtreqless 0.$$

This leads to a consideration of the function

$$f(x, y) = 2Nxy - [(N-S_1)^2+(N-S_2)^2]x - (S_1^2+S_2^2)y \gtreqless 0$$

This function is represented in three dimensions by a hyperbolic paraboloid, a saddle-shaped figure, whose trace in the xy plane is the hyperbola $f(x, y)=0$. Between the two branches of this hyperbola $f(x, y)<0$ hence $t_1<t_2$ for all values of (x, y) in this region.

In an actual situation, x must be less than the minimum of S_1 and S_2. Assume the minimum $(S_1, S_2)=S_1$. Then $x<S_1$. Also y must be less than the minimum of $N-S_1$ and $N-S_2$. If $S_1<S_2$ then minimum $(N-S_1, N-S_2)=N-S_2$ and $y<N-S_2$. Hence, $x+y<N-(S_2-S_1)$. It is now necessary to investigate the intersections of

$$2Nxy-[(N-S_1)^2+(N-S_2)^2]x-(S_1^2+S_2^2)y=0$$

with

$$x+y=N-(S_2-S_1)$$

by solving the two equations simultaneously.

The solution leads to the discriminant $8N(S_2-S_1)\ [S_1^2-S_2^2-N(S_1+S_2)]$, which is obviously negative for $S_1<S_2$. It may be shown also that the same conclusion holds if $S_1>S_2$. Therefore, there are no real points common to the two loci and hence $t_1<t_2$ for *all* practical values of x and y.

The following examples, one in which $x=y$ and the other where $x\neq y$ illustrate the point:

Example I

Series A:
- Number of patients = 50
- Number surviving five years = 20
- Number who would have lived without treatment = 5
- Number who would have died regardless of type of treatment received = 5

Series B:
- Number of patients = 50
- Number surviving five years = 40
- Number who would have lived without treatment = 5
- Number who would have died regardless of type of treatment received = 5

The calculation of t_1 which disregards x and y, gives the value 4.47 while t_2, which excludes x and y gives 5.39. Then $t_1<t_2$.

Example II

Series A:
- Number of patients = 50
- Number surviving five years = 24
- Number who would have lived without treatment = 4
- Number who would have died regardless of type of treatment received = 12

Series B:
- Number of patients = 50
- Number surviving five years = 20
- Number who would have lived without treatment = 4
- Number who would have died regardless of type of treatment received = 12

The calculations of t_1 gives 0.81 while $t_2=0.98$ and again $t_1<t_2$.

This discussion of the use of Student's t-test in the assessment of two forms of treatment indicates that the sensitivity of the test decreases when no consideration is given to the number of individuals in each group who would have lived without treatment and those who would have died regardless of the type of treatment received. The t-test, then, might lead to the conclusion that no significant difference exists between two forms of treatment when a real difference might be present but in no instance would the t-test indicate a significant difference when none exists. The error in the use of the test is therefore a conservative one.

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VOL. 75, NO. 3

NEUTRON CAPTURE THERAPY: SLOW NEUTRON DEPTH DISTRIBUTION MEASUREMENTS IN TISSUE*

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BASIS OF NEUTRON CAPTURE THERAPY

PHYSICAL Considerations. Neutron capture therapy is a radiation treatment which uses energetic heavy particles created inside the disease site.[1,7] It is based on localizing a suitable target or capture isotope in the intended site of treatment and then directing a stream of slow neutrons through that region. The localization of the radiation and the high biological effectiveness of heavy particles are two of its chief advantages.

The energy of a thermal neutron is very low, about 0.025 electron volts for one in the thermal energy range, and it has negligible direct effect in tissue. When such a neutron is captured by the target element, however, millions of electron volts of nuclear energy are released, carried by the heavy particles resulting from the breakup of the unstable intermediate nucleus.

The experimental work on this mode of treatment reported previously[2,4] employed the boron isotope of mass 10 for the capture element. In this reaction the neutron and the B^{10} nucleus combine momentarily to form an unstable compound nucleus. This resulting complex immediately decays with the production of two particles, an alpha particle (or helium nucleus) and a lithium particle. In writing the nuclear equation for this reaction[3,6,9] (Table 1), the mass balance shows 0.00300 atomic mass units converted into nuclear energy. Theoretical and experimental determinations both give the value 2.79 million electron volts (mev.) for the energy released. In 92 per cent of the events, however, the Li^7 nucleus is left in an excited state, withholding from the energy available for motion of the particles almost 0.48 mev., which it then gives up in the form of a gamma ray (Fig. 1). The 2.31 mev. remaining is divided between the two heavy particles giving them equal and opposite momentum.[3] From the point of origin, they travel in nearly opposite directions delivering their energy along a path some 14 microns in length. In the 8 per cent of the events which do not produce the gamma ray, the path of ionization is slightly longer.

TABLE 1

MASS ENERGY RELATIONS IN B(n, α) Li REACTION

$_5B^{10} + _0n^1 \rightarrow _5B^{11*} \rightarrow _2He^4 + _3Li^7 + 2.79$ mev.

Nuclides	Masses in a.m.u.	
$_5B^{10}$	10.01611	
$_0n^1$	1.00898	
$_5B^{10} + _0n^1$		11.02509
$_2He^4$	4.00387	
$_3Li^7$	7.01822	
$_2He^4 + _3Li^7$		11.02209
Net mass difference		0.00300

* From the Einstein mass-energy relation $E = mc^2$, 0.00300 atomic mass units is equivalent to 2.79 million electron volts.

Physiologic Basis: Selective Kinetics. The localization of the target element in the tumor to be treated utilizes the selective kinetics of borax, a phenomenon which is based on the natural difference in rate of uptake between tumor and normal tissue. The experimental series reported in 1954[2] applied this procedure in the treatment of the malignant brain tumor, glioblastoma

* This research was supported by the Atomic Energy Commission. Presented at the Thirty-sixth Annual Meeting of the American Radium Society, Hot Springs, Virginia, March 14–16, 1954.

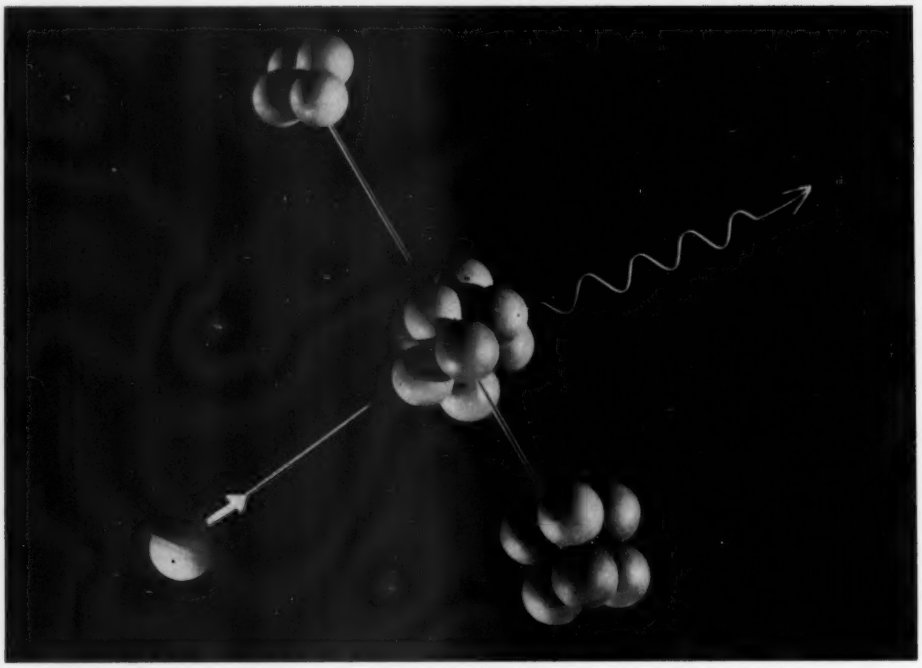

FIG. 1. Model of the nuclear reaction of slow neutron capture in B^{10} with disintegration into alpha and lithium particles and gamma emission.

multiforme. Following injection of B^{10} (as borax) into the blood stream, the concentration of boron in tumor rises rapidly to the level in the blood while the normal portion of the brain excludes the boron. The uptake curves in Figure 2 show schematically this lag in uptake. The lag may be attributed to the so-called blood-brain-barrier which excludes most foreign elements from the brain. This barrier does not exist in the tumor region. Probably the enhanced vascularity of the tumor also aids in the concentration differential which is shown. This figure is presented only schematically, since the curves vary from one subject to another both in time scale and in the ratio of concentrations. Application of the neutron beam for treatment is arranged to take advantage of the time interval of most favorable difference.

REACTOR FACILITY

The nuclear reactor or chain reacting pile is the only source now available which can supply an adequate flux of slow neutrons for this experiment. The design of the research reactor at Brookhaven is the first to provide massive beams of neutrons external to the reactor itself. The unique feature which makes this possible is the removable shielding blocks in the roof section of the biological shield. The photograph of a model of the reactor (Fig. 3)

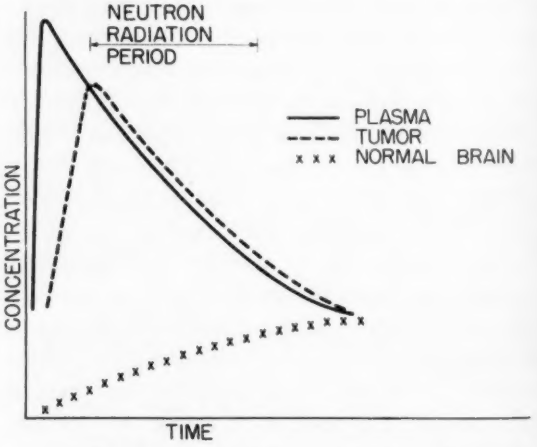

FIG. 2. Hypothetical concentration curves for boron in blood, normal brain and tumor.

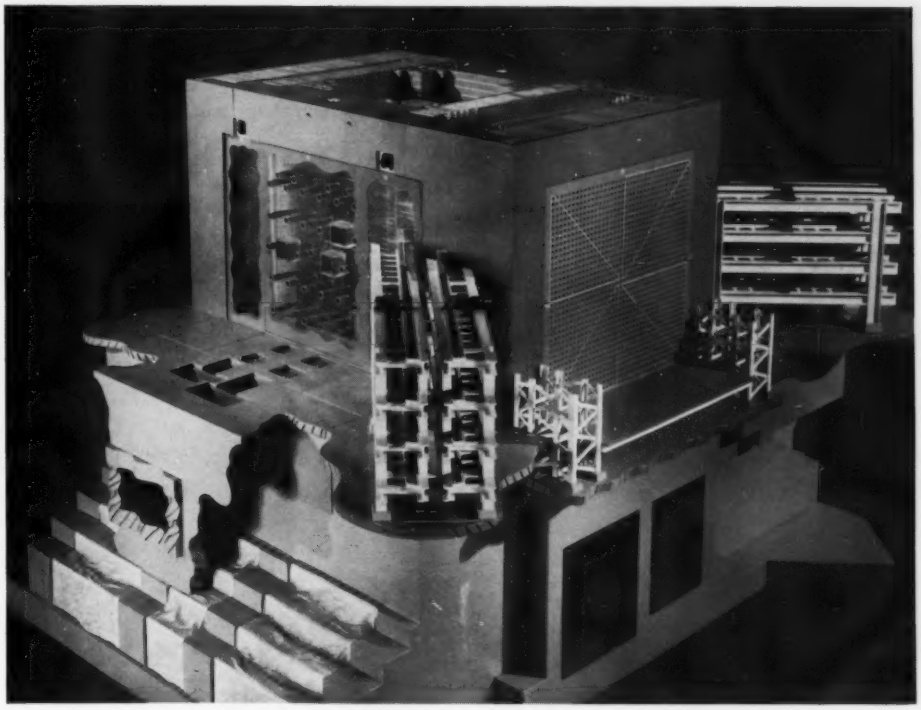

FIG. 3. Model of the Brookhaven research reactor showing removable top shielding blocks.

shows the blocks and many other special facilities built in to make it a flexible research machine.

Nuclear fission in the reactor releases fast neutrons. To provide slow neutrons, graphite in the surrounding reflector or a thermal column moderates the neutrons and brings their energy down from the many millions of electron volts with which they are created to the fraction of an electron volt which they must have in order to mediate the desired reaction.

A section through the treatment facility which has been used is shown in Figure 4. At this treatment site there are the slow neutrons that we desire, many fast neutrons which still have not been slowed down to thermal energies, and a quantity of gamma radiation originating in the fission process which is the source of reactor power. In spite of countermeasures against the unwanted radiations, they are still present in appreciable quantities. A heavy bismuth shield was used to filter out most of the gamma radiation in this facility. The fast neutron contamination is adequately low at this site.

DOSIMETRY

The dosimetry of this mixed radiation beam is complex. The energy delivered to tissue by the nuclear reaction which is the basis of the rationale must be calculated from the slow neutron flux throughout the irradiated region and the corresponding boron concentration.

Slow neutrons *per se* have negligible effect in passing through tissue. However, while the fast neutrons and pile gamma radiation contribute to the total radiation in the treatment area, still other adventitious radiations result from the passage of slow neutrons through tissue. The important reactions here are the capture of slow neutrons in nitrogen giving a short range but energetic proton and the capture in hydrogen giving a gamma ray. The intensities of these vary from point to point

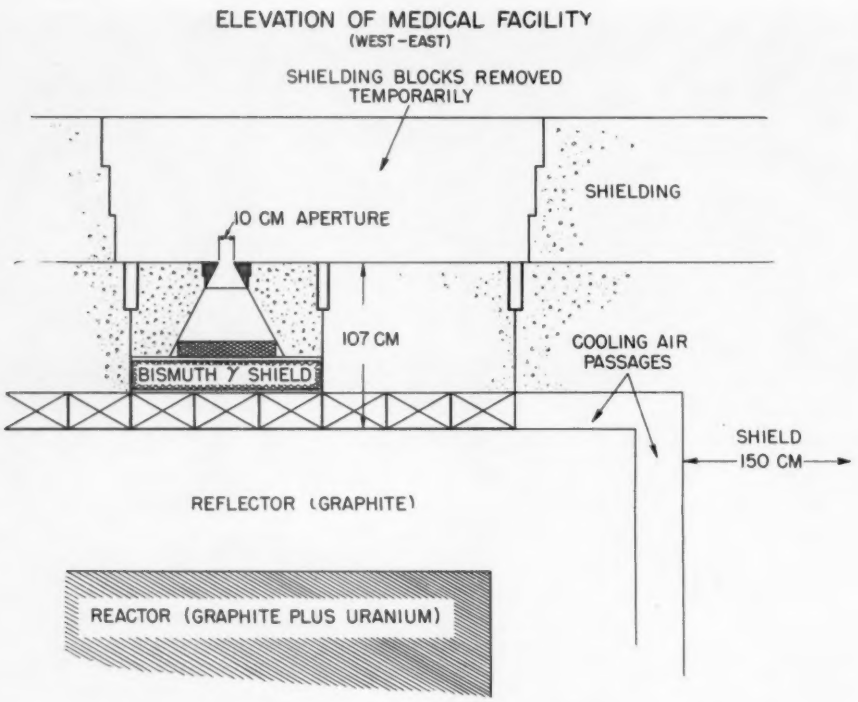

Fig. 4. Cross section of the original medical treatment facility on the reactor.

because of great differences in slow neutron flux as demonstrated in this investigation. The report of Javid, Brownell and Sweet,[5] while recognizing this effect, does not take it into account in dosage calculations.

The alpha and lithium particle radiation produces the desired differential therapeutic effect, because of its greater concentration in the affected regions. Because of their limited penetration, these particles are absorbed in the immediate vicinity of their origin. An ideal answer to the dosimetry problem would be a surgical-type probe counter sensitive to these radiations, to be inserted into the region during treatment. Neither ionization chambers nor Geiger tubes seem to hold any promise in this respect, because the short range particles cannot penetrate their wall structures. Efforts have been made and are continuing, however, toward utilization of scintillation crystals or crystal conduction detectors which might be held in intimate contact with the tissues during irradiation. The probe has usually been in the form of a light pipe tipped with an alpha-sensitive phosphor leading out to the photomultiplier tube near the patient's head. Probably the chief obstacle to its success is the presence of relatively high levels of gamma radiation, both from the core of the reactor and from local reactions with slow neutrons, which interfere with the operation of this type of detector. If such an instrument can be successfully developed, it might be utilized to aid in the converse problem of determining the concentration of the capture element in the region during treatment.

Since the heavy particle dose cannot yet be measured directly, it must be calculated from a knowledge of the neutron flux density and the boron concentration in the tissues. The boron concentration is found from studies of the physiological kinetics of the uptake of the element and from consideration of the quantity injected. Values of the neutron capture cross section and the energy emitted are taken from the physical literature. In each particular experiment the neutron flux incident on the skin of the patient is known from pile

operation characteristics and from monitoring devices; it is also calculated from the activation of gold foils exposed on the "temples" and on the port.

NEUTRON FLUX DENSITY MEASUREMENTS

Neutron Detection Methods. Neutrons cannot be detected or measured directly in their own right. All methods depend on the observation of some secondary effect resulting from the action of the neutrons, since neutrons do not have the electrical charge which is utilized for detecting other particulate radiations. The effects chiefly useful for slow neutrons are the radioactivity induced in a target or foil material and the fission effect which follows neutron capture in certain heavy elements. The energetic proton recoil in hydrogenous material can be used for fast neutrons. The difference in fissioning characteristics for fast or slow neutrons, as shown by U^{235} and U^{238}, is applied in special differential ionization chambers. Photographic films are also used; here again, the proton recoil or a capture reaction provides the ionizing radiation which is necessary to expose the films.

An experiment corollary to these studies uses the activity resulting fron neutron capture by B^{10} in tissue specimens, recorded on nuclear track emulsions, to determine the localization and quantitation of the capture element on a cytological scale.

For the present purpose, the foil activation method is convenient in many ways. Various materials can be used as foils. They can be selected to provide slow or rapid activation as may be desired and to be responsive to neutrons of specific energy ranges within limits. Figure 5 shows the dependence of the capture probability on neutron energy for certain materials, including the capture element, B^{10}, and gold. The cadmium data are shown, since they can be used to get a correction factor, minimizing the influence of the characteristic peak in the gold curve.

The characteristic behavior of gold in this resonance range weights its response in the presence of neutrons somewhat "harder" than thermal. An index of the quality of the beam can be taken as the ratio of activation of foils with and without cadmium filters.

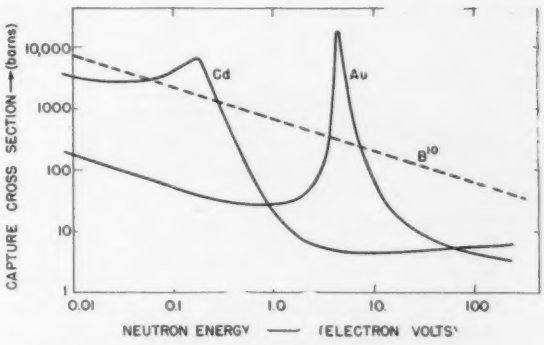

FIG. 5. Dependence of capture cross section on neutron energy.

The use of gold or other foils to detect neutrons avoids the difficulty of interference from contaminating radiations which is inherent in ionization methods. Detection methods depending on ionization are affected to greater or lesser degree by each component of the mixed radiation beam as well as by radioactivity generated within the instrument itself. Foils can be made to any desirable size or shape. Here very thin disks were used with the total mass so small that the "foil drain" loss is negligible within the limits of the experiment. Pure gold of 0.025 mm. thickness was used in uniform disks of 5.58 mm. diameter. The ordinary physical properties of gold make it especially suitable for use as intracranial foils in the form of solid gold wire.[8]

Tissue-Equivalent Phantoms. Suitable phantoms have been made in the form of aqueous solutions, semisolid gel mixtures, and plastics. The characteristic scattering and capture reactions between neutrons and the constituents of tissue which account for the more important reactions require that the phantom should closely match tissue not only in density but also in the proportions of the several chemical elements. The aqueous solutions

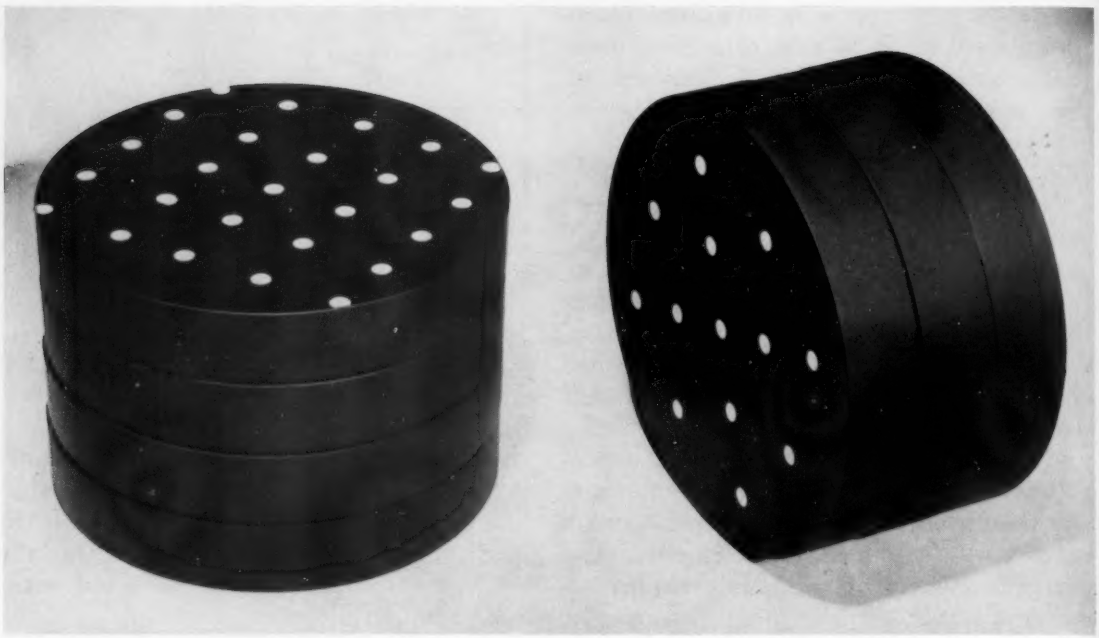

FIG. 6. Tissue-equivalent plastic phantom showing disposition of gold foils throughout the mass.

have nearly correct density, but a close density match is not easy to achieve with plastics. The atomic populations can be adjusted readily in liquids, but the plastics must be especially compounded and processed. The material used here was developed for instrumentation applications by the Radiological Research Laboratory at Columbia University.

The neutron flux distribution curves, which were formulated to evaluate the radiation pattern in the brain tumor treatment experiments, were obtained by using a plastic phantom consisting of 7 disks, each 1 inch in thickness and 6 inches in diameter. They were stacked to form a right circular cylinder somewhat larger and somewhat more solid than a normal head. Throughout this mass, shown partly assembled in Figure 6, gold foils were distributed on a 1-inch module in the 3 orthogonal directions, with additional foils interspersed in regions of higher gradient. The phantom was irradiated at the medical facility on top of the reactor for approximately the same total dose as was used in the experimental treatment; that is, about 10^{12} neutrons per cm.^{2} on the presented surface. The treatment port used in the first series of experiments was 2 by 4 inches. The long axis of the cylinder was parallel to the long axis of the port.

Arrangement of Foils. About 120 foils were used in each phantom irradiation. It is noteworthy that a major advantage of the foil method is the ease with which identical irradiations can be obtained in the phantom; they are done simultaneously. The smallness and simplicity of the detectors make it entirely possible to do a complete survey from a single exposure. Subsequently, the radioactivity of each foil was counted at convenient times. Corrections were made for counting (dead-time) losses, background, and radioactive decay from the end of the exposure to the time of counting. Standard procedure for precision beta counting was followed. Later work has been done with gamma counting in a well-type scintillation counter.

The radioactive buildup and decay characteristics of gold are used to calculate the neutron flux. If it is assumed that the neutron flux during the exposure was constant, the fraction of saturation activity reached during the exposure can be taken

from the usual radioisotope production formula. This provides a buildup factor which can be applied to give the counting rate which would be reached if the exposure were prolonged to saturation. To find the flux during the experiment, this result is then compared with the value obtained from similar foils exposed to saturation activity in a calibrated standard neutron source. Calibration has also been based on exposure at a given position with an absolute ionization instrument utilizing a fission plate activated by the same slow neutron flux.

NEUTRON DEPTH DOSE DIAGRAMS

The results of these measurements and calculations were plotted to show the flux density values along straight lines in the 3 directions; from these plots, the locations of isoflux points were interpolated. These points were used to draw up complete sets of isoflux contours in planes orthogonal and parallel to the beam axis. As an example, Figure 7 gives measurements from foils exposed in the phantom along the central axis of the treatment port. Note that this is a semilogarithmic plot. Cross-interpolation from such depth curves in the longitudinal and transverse planes provided the points from which the isoflux contours shown in Figure 8 were plotted. Figure 9 shows the pattern in the vertical plane through the long axis of the phantom. In Figure 10, the application of this information to the treatment situation is shown in an idealized manner to illustrate space relationships during the experiment.

There is a nearly exponential decrease in neutron density along the beam axis. When plotted, it shows a half-value layer for the material of 1.65 cm. Correction for the density (1.12) of the plastic gives an approximate figure for true tissue-equivalent material of 1.85 cm., more nearly matching values from theoretical work and other experimental work. In view of the diffuse nature of the stream of neutrons used in this study, this value might be expected to fall somewhat below such values specified for "broad beam" conditions.

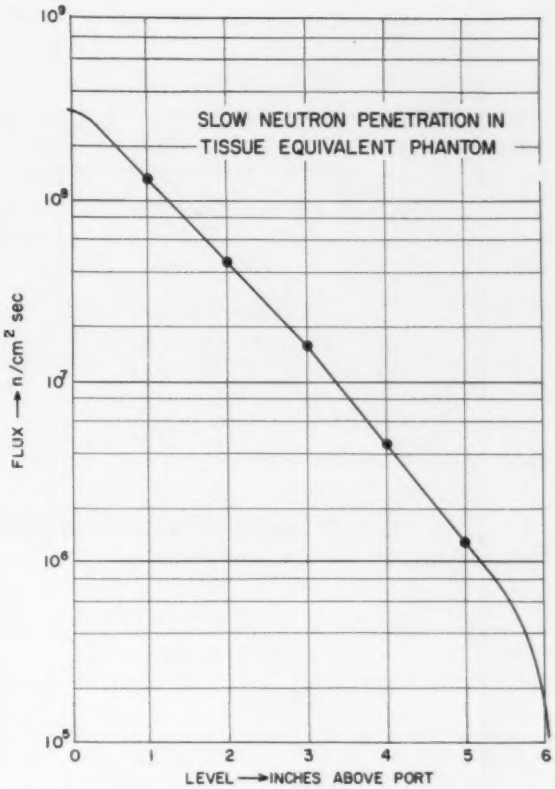

Fig. 7. Penetration of slow neutrons along central axis of the treatment port.

DISCUSSION

There are several characteristic differences between these patterns of neutron penetration and the type of pattern which is familiar from other clinical and experimental radiation beam sources. First, this source is not properly a beam; it is not collimated nor does it diverge from a point. In order to achieve a sufficient quantity of neutrons for therapeutic purposes, the facility at the reactor had to be built in the shape of an inverted cone, "funneling" neutrons from a large area of reactor surface through a small treatment aperture.

A second major difference is in the size of the steps between isoflux lines. Ordinarily, the pattern of graduations in a roentgen-ray depth dose diagram is an orderly progression of steps of 5 or 10 per

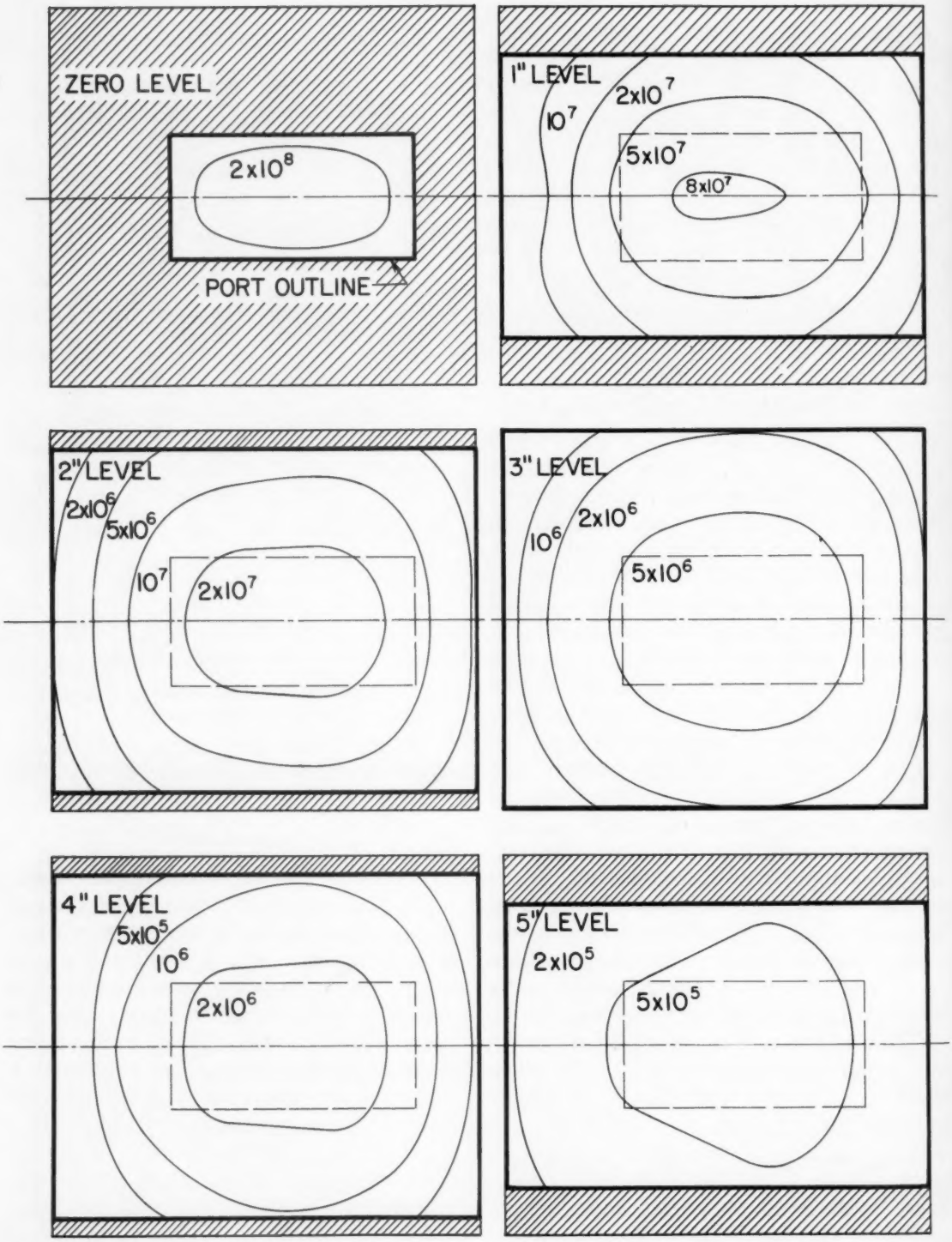

FIG. 8. Slow neutron isoflux contours in tissue-equivalent plastic phantom at distances above the treatment port as indicated. These contours are interpolated from activation of gold foils exposed on these horizontal levels, and are the basis of interpolation for vertical neutron penetration curves.

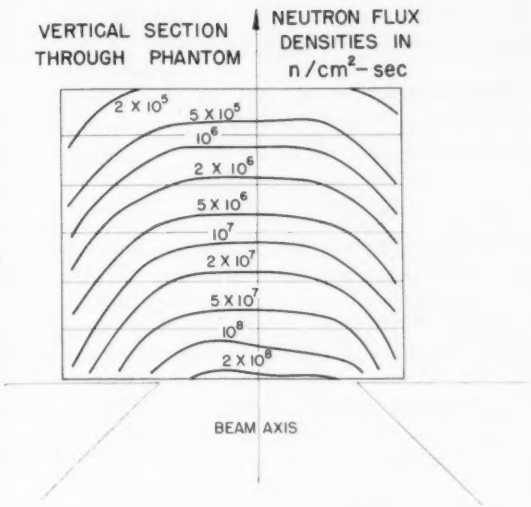

FIG. 9. Vertical penetration of neutrons through phantom on beam axis.

cent, falling off to perhaps one tenth the initial intensity in going through the thickness of a normal head, for roentgen rays of half-value layer about 1.5 mm. of copper. Electron beams penetrate with roughly uniform energy delivery for a certain distance controlled by the accelerator voltage, with sudden fall off to zero at the end of that range. In contrast, neutrons of thermal or near thermal energies pervade tissue more like a gas, being scattered by collision with atomic nuclei (principally hydrogen) and eventually being captured; the most important nuclei in this sense are hydrogen and nitrogen. The result is that a half-value layer of tissue is of the order of 2 cm. Because of the diffuse or nonbeam nature of the stream of neutrons used here, the fall-off is even more rapid and there is a difference by a factor of a thousand between the incident and the emergent neutron flux densities. An essentially logarithmic depth distribution is shown.

The radiation dose delivered to tissue has been plotted as a function of depth for

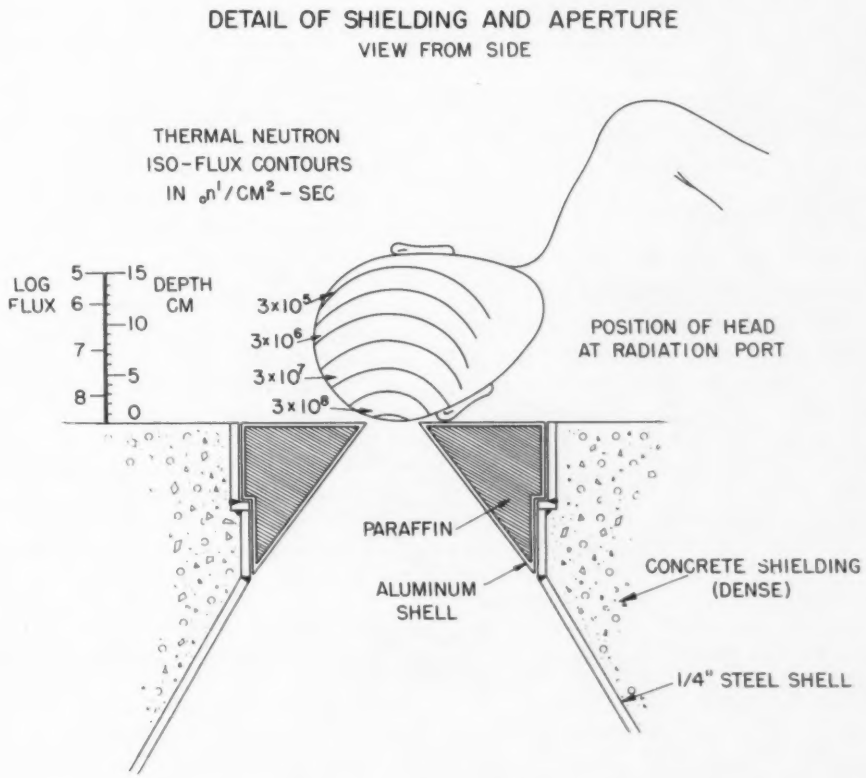

FIG. 10. Idealized schematic drawing showing isoflux contours projected on head in position at the treatment port.

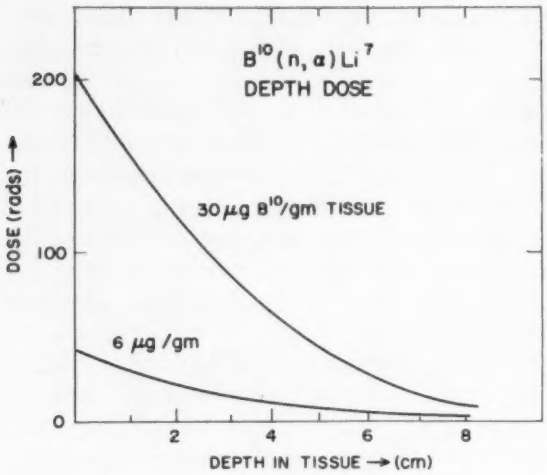

FIG. 11. Calculated depth dose.

B^{10} concentrations, as shown in Figure 11. This is for a typical experiment, where 10^{12} neutrons per cm.^{2} is the total quantity administered at the skin. At a depth of 2.5 cm., 1 gm. of tissue bearing 30 μg. of B^{10} receives 100 rads of radiation energy. At the same depth, a tissue which bears only 6 μg. of B^{10} receives 20 rads. This is about one third the dose received by similar tissues at the surface and about ten times that delivered at the midline.

SUMMARY

The general pattern of slow neutron penetration has been determined by the use of foil activation techniques in phantoms having neutron-sensitive characteristics equivalent to tissue. The patterns are applicable in a strict sense only to the experimental facility where they were made. They are, at present, the best data available for calculation of the heavy particle radiation dose in the neutron capture therapy experiment.

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Vol. 75, No. 3

THE AMERICAN JOURNAL OF ROENTGENOLOGY, RADIUM THERAPY AND NUCLEAR MEDICINE

Editor: Lawrence Reynolds, M.D.

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Published by: Charles C Thomas, Publisher, 301–327 East Lawrence Avenue, Springfield, Illinois.

Issued monthly. Annual subscription: United States, Mexico, Cuba, Central and South America, $15.00; Canada, $16.00; other countries, $17.00. Current single numbers, $1.50. Advertising rates submitted on application. Editorial office, 110 Professional Building, Detroit 1, Michigan. Office of publication, 301–327 East Lawrence Avenue, Springfield, Illinois. Information of interest to authors and readers will be found on page vi.

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Editor: Lawrence Reynolds, 110 Professional Building, Detroit 1, Mich.

Fifty-seventh Annual Meeting: Statler Hotel, Los Angeles, Calif., September 25–28, 1956.

AMERICAN RADIUM SOCIETY

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Thirty-eighth Annual Meeting: Shamrock Hotel, Houston, Texas, April 9–11, 1956.

EDITORIALS

THE THIRTY-EIGHTH ANNUAL MEETING OF THE AMERICAN RADIUM SOCIETY

THIS year will mark the sixtieth year since A. H. Becquerel discovered that uranium compounds emit radioactive radiations. One year earlier W. C. Röntgen demonstrated a peculiar phenomenon which he called "X-rays." Marie and Pierre Curie announced the discovery of "polonium" in July and of "radium" in December, 1898. In 1906 The American Journal of Roentgenology, Radium Therapy and Nuclear Medicine, then called "The American Quarterly of Roentgenology," was established as an outlet for the pioneer work being done in radiology. Forty years ago the American Radium Society was founded by an active and elite group of practicing physicians who were becoming increasingly aware of the value of ionizing radiation in the treatment of disease. Dr. James T. Case, one of the two charter members, I am happy to say, is still very active in this great Society. Dr. Case became Editor of the Journal in 1916, the same year that he was elected to membership in the Society. Since that time most of the papers of the American Radium Society have been published in The American Journal of Roentgenology, Radium Therapy and Nuclear Medicine; thus, it is only natural that the Journal should have become the official Journal of the American Radium Society. The association with the American Roentgen Ray Society and the Journal has been most cordial. Progress has been the theme. I am amazed at the advancement that has taken place in the few short years since the discovery of radium and roentgen rays. The programs of this Society and the papers published in the Journal have been filled with new discoveries and new techniques towards prolonging life and making living easier.

The Thirty-eighth Annual Meeting of the American Radium Society is to be held at the Shamrock Hotel in Houston, Texas, Monday, Tuesday and Wednesday, April 9, 10 and 11, 1956. Registration will be from 3:00 to 5:00 P.M. Sunday, April 8, and begin at 9:00 A.M. Monday, April 9. The scientific program of this unique Society will contain fifteen individual papers, two symposia and twelve round table discussions.

The individual presentations will encompass all phases of modalities of treatment of cancer, as well as new research in the physical application. These papers will be given Monday and Tuesday forenoons at the Shamrock Hotel.

The symposia, which will be held Monday and Tuesday afternoons, will cover two of the most important controversial subjects in cancer therapy: "Choice and Timing of Palliative Procedures for Advanced Breast Carcinoma" and "Cancer of the Thyroid Gland." Dr. Joseph H. Farrow and Dr. Edgar L. Frazell will moderate these symposia.

A somewhat different approach will be pursued Wednesday morning at the M.D. Anderson Hospital. There will be twelve round table discussions, each of one hour's duration. Simultaneously there will meet six different round table groups, each limited to twenty persons. Such timely subjects as cancer of the breast, mouth, cervix, lung, thyroid, larynx, and the lymphomas will be discussed. Hazards of isotopes and cobalt beam therapy will compose a very important part of these round table discussions. Outstanding leaders in the various fields will direct these discussions and

group members are urged to participate. Each member or guest may thus have a choice of two of these groups. Members of the Society will be canvassed before the meeting for their two choices. At eleven A.M., after the round table discussions, tours of the M. D. Anderson Hospital will be conducted for those who desire to observe the functioning of this remarkable Institution.

The Janeway Lecture will be presented by Dr. Lloyd F. Craver, Director of Medicine of Memorial Hospital, New York. Dr. Craver has long been recognized as the outstanding authority on lymphomas. He has contributed much to the literature and his observations on this disease have been long looked upon as "a sort of bible."

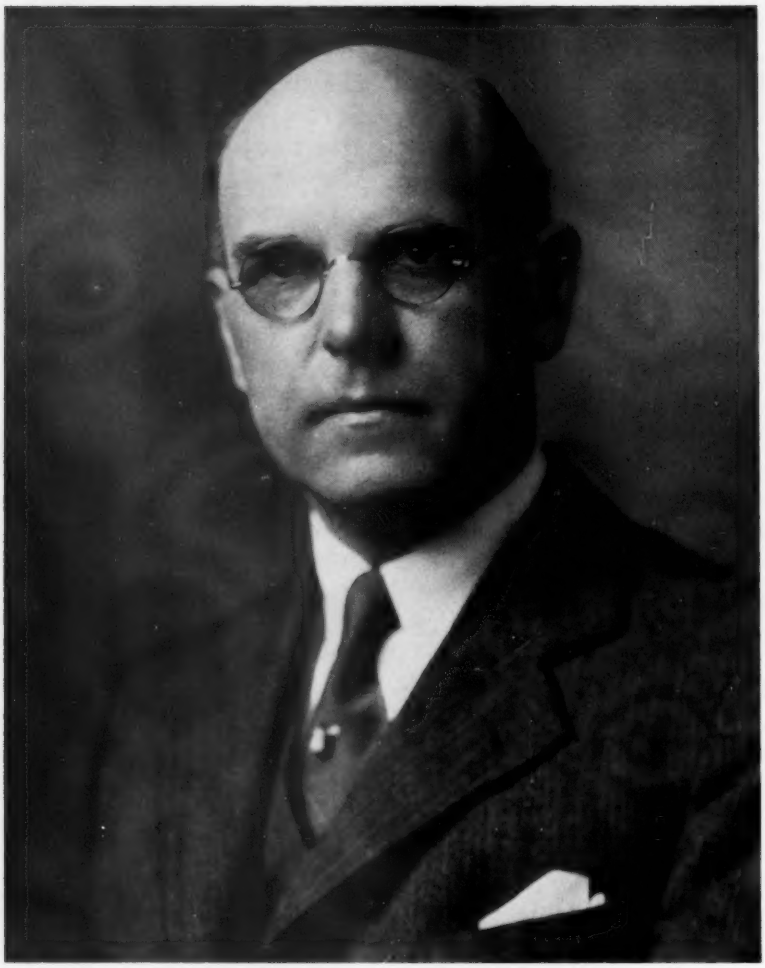
The Arrangements Committee will entertain at a cocktail party for members Sunday evening, April 8. The Radium Chemical Company will give a cocktail party Monday evening preceding the Janeway Lecture and dinner. The annual banquet will be Tuesday night.

The program will be full. The Shamrock Hotel offers excellent shopping centers and recreational facilities for the ladies. Luncheons and tours of interesting sections of Houston and surrounding countryside will be conducted. We hope all members will be able to attend this fine program and partake of our Houston friends' hospitality. All members of the profession interested in cancer are invited.

A preliminary program appears in this issue of the Journal. Members have also received a preliminary program by mail. Reservations should be made directly with the Shamrock Hotel, Houston, Texas, indicating they are for the meeting of the American Radium Society. Members have received information regarding air travel. Houston is an important center, and easy to reach from anywhere in the United States. Further information for members or guests may be obtained from the Secretary of the American Radium Society, Robert E. Fricke, Mayo Clinic, Rochester, Minnesota, or from Dr. William S. MacComb, Chairman of the Committee on Arrangements, M. D. Anderson Hospital, Houston, Texas.

Grant Beckstrand, M.D., *President*
American Radium Society

1090 Atlantic Avenue
Long Beach, California



HARRY H. BOWING
1884–1955

THERAPEUTIC radiology lost an eminent practitioner and teacher with the death of Harry H. Bowing, December 7, 1955, at San Mateo, California.

Associated with him from 1927 until his retirement, caused by a severe stroke in 1948, I could well appreciate that besides being a marvelous teacher he was an outstanding practitioner of the art, as well as the science, of medicine. His patience, his sympathetic attitude, and his conscientious attention to all details of his work endeared him to all his patients and associates.

He was a past-president of the American Radium Society and an active member of the American Roentgen Ray Society, the Radiological Society of North America, the American Medical Association, the Alumni Association of the Mayo Foundation and the Society of Sigma Xi.

Harry H. Bowing was born on July 22, 1884, at Richmond, Indiana. He received the degree of B.S. in 1913 from Earlham College, Richmond, Indiana, and of M.D. in 1917 from the University of Pennsylvania, and was an intern at St. Joseph's Hospital in Philadelphia from 1917 to 1918. In June, 1919, he became head of the Section of Radium Therapy of the Clinic, and he held this post until July, 1948, when he became a senior consultant in the same section. He was appointed an instructor in radiology in the Mayo Foundation, Graduate School, University of Minnesota, in 1922; assistant professor in 1929; associate professor in 1933, and full professor in 1936.

ROBERT E. FRICKE, M.D.

SOCIETY PROCEEDINGS, CORRESPONDENCE AND NEWS ITEMS

MEETINGS OF RADIOLOGICAL SOCIETIES*

United States of America

American Roentgen Ray Society
Secretary, Dr. Barton R. Young, Germantown Hospital, Philadelphia 44, Pa. Annual meeting: Statler Hotel, Los Angeles, Calif., Sept. 25–28, 1956.

American Radium Society
Secretary, Dr. R. E. Fricke, Mayo Clinic, Rochester, Minn. Annual meeting: Shamrock Hotel, Houston, Texas, April 9–11, 1956.

Radiological Society of North America
Secretary, Dr. D. S. Childs, 713 E. Genesee St., Syracuse 2, N. Y. Annual meeting: Palmer House, Chicago, Ill., Dec. 11–16, 1955.

American College of Radiology
Executive Secretary, William C. Stronach, 20 N. Wacker Drive, Chicago 6, Illinois. Annual meeting: 1956, to be announced.

Section on Radiology, American Medical Association
Secretary, Dr. T. Leucutia, Harper Hospital, Detroit 1, Mich. Annual Meeting: June 11–15, 1956, Chicago, Illinois.

Eighth International Congress of Radiology
Secretary General, Dr. José Noriega, Calle del Oro 15, Mexico 7, D. F. Meets Mexico City, July 22–28, 1956.

Alabama Radiological Society
Secretary, Dr. J. A. Meadows, Jr., Medical Arts Bldg., Birmingham 5, Ala. Meets time and place Alabama State Medical Association.

Arizona Radiological Society
Secretary, Dr. J. J. Riordan, 550 W. Thomas Rd., Phoenix, Ariz. Two regular meetings a year. The annual meeting at time and place of State Medical Association and interim meeting six months later.

Arkansas Radiological Society
Secretary, Dr. J. A. Norton, 843 Donaghey Bldg., Little Rock, Ark. Meets every three months and also at time and place of State Medical Association.

Association of University Radiologists
Secretary, Dr. Robert J. Bloor, 260 Crittenden Blvd., Rochester 20, New York. Annual meeting, May, 1956 at the University of Rochester, N.Y.

Atlanta Radiological Society
Secretary, Dr. Charles M. Silverstein, 3254 Peachtree St., N.E., Atlanta, Ga. Meets monthly, except during three summer months, on second Friday evening.

Blockly Radiological Society
Secretary, Dr. Samuel Finkelman. Annual dinner: May, 1956.

Brooklyn Radiological Society
Secretary, Dr. Theodore Kamholtz, 152 Clinton Street, Brooklyn, N. Y. Meets first Thursday of each month October through May.

Brooklyn Roentgen Ray Society
Secretary, Dr. J. J. Daversa, 345 75th St., Brooklyn, N. Y. Meets monthly fourth Tuesday, October through April.

Buffalo Radiological Society
Secretary, Dr. Clayton G. Weig, 135 Linwood Ave., Buffalo, N. Y. Meets second Monday evening each month, October to May inclusive.

Central New York Roentgen Ray Society
Secretary, Dr. Dwight V. Needham, 608 E. Genesee St., Syracuse, N. Y. Meets January, May, November.

Central Ohio Radiological Society
Secretary, Dr. Arthur R. Cohen, 41 S. Grant Ave., Columbus, Ohio. Meets at 6:30 P.M. on second Thursday of October, November, January, March and May at Fort Hayes Hotel, Columbus, Ohio.

Chicago Roentgen Society
Secretary, Dr. E. Burns Lewis, 670 N. Michigan Ave., Chicago 11, Ill. Meets second Thursday of each month, October to April inclusive at the Sheraton Hotel.

Cleveland Radiological Society
Secretary, Dr. A. S. Tucker, 2020 East 93 St., Cleveland 6, Ohio. Meetings at 7:00 P.M. on fourth Monday of each month from October to April at Tudor Arms Hotel.

Colorado Radiological Society
Secretary, Dr. Dorr H. Burns, 1776 Vine St., Denver, Colo. Meets third Friday of each month at University of Colorado Medical Center or at Denver Athletic Club.

Connecticut Valley Radiologic Society
Secretary, Dr. T. J. Crowe, 53 Center St., Northampton, Mass. Meets second Friday October and April.

Dallas-Fort Worth Radiological Club
Secretary, Dr. A. H. Keene, 3707 Gaston Ave., Dallas, Texas. Meets monthly, third Monday, at Greater Fort Worth International Airport at 6:30 P.M.

Detroit Roentgen Ray and Radium Society
Secretary, Dr. E. F. Lang, Harper Hospital, Detroit, Mich. Meets monthly first Thursday, Oct. through May at David Whitney House, 4421 Woodward Ave., at 6:30 P.M.

East Bay Roentgen Society
Secretary, Dr. Dan Tucker, 434 30th St., Oakland 9, Calif. Meets first Thursday each month at Peralta Hospital, Oakland.

Florida Radiological Society
Secretary, Dr. D. H. Gahagen, 320 Sweet Bldg., Fort Lauderdale, Fla. Meets twice annually, in the spring with the annual State Society meeting, and in the fall.

Georgia Radiological Society
Secretary, Dr. B. H. Malone, 1406 Reynolds St., Brunswick, Ga.

Greater Miami Radiological Society
Secretary, Dr. A. S. Capi, 300 N. 20th Ave., Hollywood, Fla. Meets monthly third Wednesday at 8 P.M. at various South Florida Hospitals.

Houston Radiological Society
Secretary, Dr. Leslie L. Lemak, 616 Medical Arts Bldg., Houston 2, Texas. Meets fourth Monday each month, Meeting Room, Doctors' Club of Houston.

Idaho State Radiological Society
Secretary, Dr. Alfred M. Stone, St. Lukes Hospital, Boise, Idaho. Meets annually at same time as Idaho State Medical Association.

Illinois Radiological Society
Secretary, Dr. Stephen L. Casper, 1101 Maine St., Quincy, Ill. Meets three times a year.

Indiana Roentgen Society
Secretary, Dr. C. A. Stayton, 313 Hume-Mansur Bldg., Indianapolis 4. Meets first Sunday in May and during fall meeting of Indiana State Medical Association.

Iowa Radiological Society
Secretary, Dr. James T. McMillan, 1104 Bankers Trust Bldg., Des Moines, Iowa. Luncheon and business meeting during annual session of Iowa State Medical Society. The scientific section is held in the autumn.

* Secretaries of societies are requested to send timely information promptly to the Editor.

Kansas Radiological Society
Secretary, Dr. A. M. Cherner, Hays, Kansas. Meets in spring with State Medical Society, and in winter on call.

Kentucky Radiological Society
Secretary, Dr. David Shapiro, 217 East Chestnut St., Louisville 2, Ky. Meets monthly on second Friday at Seelbach Hotel, Louisville.

Kings County Radiological Society
Secretary, Dr. Solomon Maranov, 1450 51st St., Brooklyn 19, N. Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:45 P.M.

Los Angeles Radiological Society
Secretary, Dr. Richard A. Kredel, 65 North Madison Ave., Pasadena, Calif. Meets second Wednesday each month at Los Angeles County Medical Association Building, Los Angeles.

Maine Radiological Society
Secretary, Dr. W. A. Russell, Augusta General Hospital, Augusta, Maine. Meets in June, October, December and April.

Maryland Radiological Society
Secretary, Dr. Paul W. Roman, 1810 Eutaw Place, Baltimore 17, Maryland.

Memphis Roentgen Society
Secretary, Dr. B. E. Greenberg, 294 Annella St., Memphis 11, Tenn. Meets first Monday of each month at John Gaston Hospital.

Miami Valley Radiological Society
Secretary, Dr. G. A. Nicoll, 134 Apple St., Dayton, Ohio. Meets second Friday of fall and winter months.

Mid-Hudson Radiological Society
Secretary, Dr. J. W. Walton, Horton Memorial Hospital, Middletown, N. Y. Meets 8:30 P.M., fourth Tuesday each month, September to May.

Milwaukee Roentgen Ray Society
Secretary, Dr. R. W. Byrne, 3321 N. Maryland Ave., Milwaukee 1, Wis. Meets monthly on fourth Monday at University Club.

Minnesota Radiological Society
Secretary, Dr. O. J. Baggenstoss, 1953 Medical Arts Bldg., Minneapolis, Minn. Meets three times annually, once at time of State Med. Assn., and in spring and fall.

Mississippi Radiological Society
Secretary, Dr. James M. Packer, 621 High St., Jackson, Miss. Meets third Thursday of each month at Hotel Edwards, Jackson, at 6:00 P.M.

Montana Radiological Society
Secretary, Dr. John Stewart, 1105 Frederick Lane, Billings, Montana. Meets at least once a year.

Nassau Radiological Society
Secretary, Dr. Frances Behrendt, 19 Clinton Rd., Garden City, N. Y. Meets second Tuesday of the month in February, April, June, October and December.

Nebraska Radiological Society
Secretary, Dr. J. F. Kelly, Jr., 816 Medical Arts Bldg., Omaha, Nebr. Meets third Wednesday of each month at 6 P.M. in Omaha or Lincoln.

New England Roentgen Ray Society
Secretary, Dr. Raymond A. Dillon, 24 Wedgemere Ave., Winchester, Mass. Meets third Friday of each month, October through May, at Hotel Commander, Cambridge, Mass.

New Hampshire Roentgen Ray Society
Secretary, Dr. A. C. Johnston, Elliott Community Hospital, Keene, N. H. Meets four to six times yearly.

New York Roentgen Society
Secretary, Dr. M. H. Poppel, 303 E. 20th St., New York 3, N. Y. Meets monthly on third Monday, New York Academy of Medicine, at 8:30 P.M.

North Carolina Radiological Society
Secretary, Dr. William H. Sprunt, North Carolina Memorial Hospital, Chapel Hill, N. C. Meets in May and October.

North Dakota Radiological Society
Secretary, Dr. Marianne Wallis, St. Joseph's Hospital, Minot, N. Dak. Meetings by announcement.

North Florida Radiological Society
Secretary, Dr. Marvin Harlan Johnston, Five Points Medical Center, Jacksonville, Fla. Meets quarterly in March, June, September and December.

Northeastern New York Radiological Society
Secretary, Dr. Robert R. Wadlund, Albany Hospital, Albany, N. Y. Meets in Albany area on second Wednesdays of October, November, March and April.

Northern California Radiological Society
Secretary, Dr. H. B. Stewart, 2920 Capitol Ave., Sacramento, Calif. Meets at dinner last Monday of each month, September to June.

Ohio State Radiological Society
Secretary, Dr. John R. Hannan, 10515 Carnegie Ave., Cleveland 6, Ohio. Annual meeting, Deshler-Hilton Hotel, Columbus, Ohio, May 12–13, 1956.

Oklahoma State Radiological Society
Secretary, Dr. John R. Danstrom, Medical Arts Bldg., Oklahoma City, Okla. Three regular meetings annually.

Oregon Radiological Society
Secretary, Dr. N. L. Bline, 210 Jackson Tower, Portland 5, Ore. Meets monthly from October to June on the second Wednesday of each month at 8:00 P.M. at the University Club.

Orleans Parish Radiological Society
Secretary, Dr. Joseph V. Schlosser, Charity Hospital, New Orleans 13, La. Meets first Tuesday of each month.

Pacific Northwest Radiological Society
Secretary, Dr. J. R. Raines, 214 Medical-Dental Bldg., Portland 5, Oregon. Meets annually in May.

Pacific Roentgen Society
Secretary, Dr. L. H. Garland, 450 Sutter St., San Francisco, Calif. Meets annually, during meeting of California Medical Association.

Pennsylvania Radiological Society
Secretary, Dr. Walter P. Bitner, 234 State Street, Harrisburg, Pa.

Philadelphia Roentgen Ray Society
Secretary, Dr. H. M. Stauffer, Temple University Hospital, Philadelphia 40, Pa. Meets first Thursday of each month, at 5 P.M., from October to May in Thompson Hall, College of Physicians.

Pittsburgh Roentgen Society
Secretary, Dr. N. Tannehill, 500 Penn Ave., Pittsburgh 22, Pa. Meets second Wednesday of month, October through June at Hotel Roosevelt.

Radiological Section, Baltimore Medical Society
Secretary, Dr. Paul W. Roman, 1810 Eutaw Place, Baltimore 17, Md. Meets third Tuesday each month, September to May, inclusive.

Radiological Section, Southern Medical Association
Secretary, Dr. Roy G. Giles, Temple, Texas.

Radiological Society of Greater Cincinnati
Secretary, Dr. R. J. Neubauer, 831 Carew Tower, Cincinnati, Ohio. Meets monthly from September to May on first Monday of each month at 7:30 P.M. at the Cincinnati General Hospital.

Radiological Society of Hawaii
Secretary, Dr. George W. Henry, 1133 Punchbowl, Honolulu, T. H. Meets third Monday evening of each month at designated hospitals.

Radiological Society of Greater Kansas City
Secretary, Dr. E. H. Stratemeier, Jr., 1010 Rialto Building, Kansas City 6, Mo. Meets last Friday of each month.

Radiological Society of Kansas City
Secretary, Dr. Arthur B. Smith, 800 Argyle Bldg., Kansas City, Mo. Meets third Thursday of each month.

Radiological Society of Louisiana
Secretary, Dr. W. S. Neal, 602 Pere Marquette Bldg., New Orleans, La. Meets annually during Louisiana State Medical Society Meeting.

Radiological Society of New Jersey
Secretary, Dr. G. G. Green, 601 Grand Ave., Asbury Park, N. J. Meets at Atlantic City at time of State Medical Society and in November in Newark, N. J.

Radiological Society of Southern California
Secretary, Dr. J. B. Irwin, 1831 Fourth Ave., San Diego, Calif.

Richmond County Radiological Society
Secretary Dr. W. F. Hamilton, Jr., University Hospital, Augusta, Ga. Meets first Thursday of each month at various hospitals.

Rochester Roentgen Ray Society, Rochester, N. Y.
Secretary, Dr. Henry H. Forsyth, Jr., 40 Meigs St., Rochester, N. Y. Meets at 8:15 P.M. on the last Monday of each month, September through May, at Strong Memorial Hospital.

Rocky Mountain Radiological Society
Secretary, Dr. John H. Freed, 4200 East Ninth St., Denver 20, Colo.

St. Louis Society of Radiologists
Secretary, Dr. Edwin C. Ernst, Jr., 3720 Washington Ave., St. Louis 8, Mo. Meets fourth Wednesday each month, except June, July, Aug. and Sept.

San Antonio-Military Radiological Society
Secretary, Dr. Hugo F. Elmendorf, Jr., 730 Medical Arts Bldg., San Antonio 5, Texas Meets Brooke Army Medical Center Officers Mess first Monday of each month.

San Diego Radiological Society
Secretary, Dr. J. C. Asher, 2001 Fourth Ave., San Diego 1, Calif. Meets first Wednesday of each month at the University Club.

San Francisco Radiological Society
Secretary, Dr. Howard L. Steinbach, University of California Medical Center, San Francisco 22, Calif. Meets quarterly at Grison's Steak House.

Section on Radiology, California Medical Association
Secretary, Dr. A. R. Wilson, 540 North Central Ave., Glendale 3, Calif.

Section on Radiology, Connecticut State Medical Society
Secretary, Dr. J. Burbank, Meriden Hospital, Meriden, Conn. Meetings are held bi-monthly.

Section on Radiology, Medical Society of the District of Columbia
Secretary, Dr. F. V. Schumacher, 1835 Eye St., N.W., Washington 6, D. C. Meets Medical Society Library, third Wednesday of January, March, May and October at 8:00 P.M.

Section on Radiology, Illinois State Medical Society
Secretary, Dr. George E. Irwin, Jr., 703 N. East St., Bloomington, Ill.

Shreveport Radiological Club
Secretary, W. R. Harwell, 608 Travis St., Shreveport, La. Meets monthly on third Wednesday, at 7:30 P.M. September to May inclusive.

South Bay Radiological Society
Secretary, Dr. T. N. Foster, 630 E. Santa Clara St., San Jose, Calif. Meets second Wednesday of each month.

South Carolina Radiological Society
Secretary, Dr. S. W. Lippincott, 103 Rutledge Ave., Charleston, S. C. One meeting with South Carolina Medical Association in May, others arranged by President.

Southwestern Radiological Society
Secretary, Dr. Gordon Black, Suite 2-A, El Paso Medical Center, 1501 Arizona, El Paso, Texas. Meets second Tuesday of each month.

Tennessee Radiological Society
Secretary, Dr. G. K. Henshall, 311 Medical Arts Bldg., Chattanooga, Tenn. Meets annually at the time and place of the Tennessee State Medical Association.

Texas Radiological Society
Secretary, Dr. R. P. O'Bannon, 650 Fifth Ave., Fort Worth 4, Texas. Next Meeting, Fort Worth, Texas, Jan. 20–21, 1956.

Tri-State Radiological Society
Secretary, Dr. E. L. Hendershot, 118 S.E. First St., Evansville, Ind. Meets last Wednesday of Oct., Jan., March and May, 8:00 P.M. at Elks' Club in Evansville.

University of Michigan Department of Roentgenology Staff Meeting
Meets each Monday evening from September to June, at 7:00 P.M. at University Hospital.

University of Wisconsin Radiological Conference
Secretary, Dr. E. A. Pohle, 1300 University Ave., Madison, Wis. Meets first and third Thursdays 4:00 to 5:00 P.M., September to May, Service Memorial Institute.

Upper Peninsula Radiological Society
Secretary, Dr. A. Gonty, Menominee, Mich. Meets quarterly.

Utah State Radiological Society
Secretary, Dr. Angus K. Wilson, 343 S. Main St., Salt Lake City 1, Utah. Meets fourth Wednesday in January, March, May, September and November at Holy Cross Hospital.

Virginia Radiological Society
Secretary, Dr. P. B. Parsons, Norfolk General Hospital, Norfolk, Va. Meets annually in October.

Washington State Radiological Society
Secretary, Dr. Eva L. Gilbertson, 1317 Marion St., Seattle 4, Wash. Meets fourth Monday of each month from September through May at 610 Pine St., Seattle.

West Virginia Radiological Society
Secretary, Dr. W. Paul Elkin, 515 Medical Arts Bldg., Charleston, W. Va. Meets concurrently with annual meeting of West Virginia State Medical Society; other meetings arranged by program committee.

Westchester Radiological Society
Secretary, Dr. M. G. Priestman, New Rochelle Hospital, New Rochelle, N. Y. Meets on third Tuesday of January and October and on two other dates.

Wisconsin Radiological Society
Secretary, Dr. W. W. Moir, 309 Geele Ave., Sheboygan, Wis. Special meetings held during year; annual meeting each spring at Madison, Wis.

X-Ray Study Club of San Francisco
Secretary, Dr. J. T. English, 2000 Van Ness Ave., San Francisco 9, Calif. Meets monthly, third Thursday at 7:45 P.M., Lane Hall, Stanford University Hospital.

Cuba, Mexico, Puerto Rico and Central America

Sociedad de Radiología y Fisioterapia de Cuba
President, Dr. J. Manuel Viamonte, Hospital Mercedes, Habana, Cuba. Meets monthly in Habana.

Sociedad Mexicana de Radiología, A. C.
Calle del Oro No. 15, Mexico 7, D. F.
Secretary General, Dr. Guillermo Santín. Meets first Monday of each month.

Asociación Puertorriqueña de Radiología
Secretary, Dr. Rafael A. Blanes, P. O. Box 9067, Santurce, Puerto Rico.

Sociedad Radiológica Panameña
Secretary, Dr. L. Arrieta Sanchez, Apartado No. 86, Panama, R. de P. Meets monthly in a department of radiology of a local hospital, chosen at preceding meeting.

British Empire

Association of Radiologists of the Province of Quebec
Secretary, Dr. Isadore Sedlezky, 3755 Cote St. Catherine Rd., Montreal, Que. Meets four times a year.

British Institute of Radiology Incorporated with the Röntgen Society
Ordinary meeting, on the Thursday preceding the third Friday, October to May at 8:15 P.M.
Medical Members' meeting, on third Friday in each month at 5:00 P.M., 32 Welbeck St., London, W 1

Faculty of Radiologists
Honorary Secretary, Dr. R. A. Kemp Harper, 45, Lincoln's Inn Fields, London, W.C.2, England.

Section of Radiology of the Royal Society of Medicine (Confined to Medical Members)
Meets third Friday each month at 4:45 P.M. at the Royal Society of Medicine, 1 Wimpole St., London.

Canadian Association of Radiologists
Honorary Secretary-Treasurer, Dr. D. L. McRae, Suite 305, 1555 Summerhill Avenue, Montreal 25, Que. Meetings January and June.

Section of Radiology, Canadian Medical Association
Secretary, Dr. C. M. Jones, Inglis St., Ext. Halifax, N. S.

Société Canadienne-Française d'Electro-Radiologie Médicales
General Secretary, Dr. Ls Ivan Vallée, 1058 rue St-Denis, Montreal 18, Canada. Meets third Saturday each month.

College of Radiologists (Australia and New Zealand)
Honorary Secretary, Dr. Alan R. Colwell, c/o British Medical Agency, 135 Macquarie St., Sydney, N.S.W.

South America

Asociacion Argentina de Radiologia
Secretary, Dr. Lidio G. Mosca, Avda. Gral. Paz 151 Córdoba, Argentina. Meetings held monthly.

Sociedad Argentina de Radiologia, Junta Central, Buenos Aires
Secretary, Dr. Oscar F. Noguera, Santa Fe 1171, Buenos Aires. Meetings are held monthly.

Sociedad Argentina de Radiologia, Filial del Litoral, Sede, Rosario
President, Dr. Francisco P. Cifarelli. Meets monthly second Wednesday, 19 ha 663 Italia St., Rosario, Santa Fe.

Sociedad Argentina de Radiologia, Filial del Sur, Sede, La Plata
President, Prof. Dr. Jose P. Uslenghi, La Plata. Meets monthly.

Sociedad Argentina de Radiologia, Filial del Centro Sede, Córdoba
President, Prof. Dr. David L. Caro, Corro 86, Córdoba. Meets monthly.

Sociedad Argentina de Radiologia, Filial del Norte, Sede, Tucuman
President, Dr. Julio Mendez Valladares, Rivadavia 358, Tucuman. Meets monthly.

Sociedad Argentina de Radiologia, Filial de Cuyo Sede, Mendoza.
President, Dr. J. A. Orfila, Hospital Central, Mendoza. Meets monthly.

Sociedade Brasileira de Radiologia Medica
Secretary, Dr. Nicola Caminha, Av. Mem. de Sa, Rio de Janeiro, Brazil. Meets monthly, except during January, February and March.

Sociedade Brasileira de Radioterapia
Secretary, Dr. Oscar Rocha von Pfuhl, Av. Brigadeiro Luiz Antonio, 644 São Paulo, Brazil. Meets monthly on second Wednesday at 9:00 p.m. in São Paulo at Av. Brigadeiro Luiz Antonio, 644.

Sociedad Colombiana de Radiologia
Secretary, Dr. Luis E. Lozano B., Carrera 12 No. 20–69, 6° piso, Bogota, Colombia. Meets last Thursday of each month.

Sociedad Ecuatoriana de Radiologia y Fisioterapia
Secretary, Dr. Enrique Ortega Guzmán, Casilla 4719, Guayaquil, Ecuador.

Sociedad Peruana de Radiologia
Secretary General, Dr. Amador Holgado V. Apartado 2306, Lima, Peru. Meets monthly except during January, February and March, at Asociación Médica Peruana "Daniel A. Carrión," Villalta, 218, Lima.

Sociedad de Radiología, Cancerología y Física Médica del Uruguay
Secretary General, Dr. Roberto Francois, Av. Agraciada 1464, Piso 13, Montevideo, Uruguay.

Sociedad Venezolana de Radiología
Secretary, Dr. Otto Paz, Centro Médico, Caracas, Venezuela. Meets monthly third Friday at Colegio Médico del Distrito Federal, Caracas.

Continental Europe

Austrian Roentgen Society
President, Dr. Konrad Weiss, Mariannengasse 10, Vienna 9, Austria. Meets second Tuesday of each month in Allgemeine Poliklinik.

Société Belge de Radiologie
General Secretary, Dr. S. Masy, 256 Chaussée de Wavre, Heverlee-lez-Louvain, Belgium. Meets monthly, second Sunday at Maison des Médecins, Brussels.

Société Française d'Electro-Radiologie Médicale, and its branches: Société du Sud-Ouest, du Littoral Méditerranéen, du Centre et du Lyonnais, de l'Ouest, de l'Est, et d'Alger et d'Afrique du Nord
Secretary-General, Dr. A. Dariaux, 9 bis, Boulevard Rochechouart, Paris IX°, France.

Ceskoslovensk společnost pro rëntgenologii a Radiologii v Praze
Secretary, Dr. Roman Bláha, Praha xii, stát. nemocnice, Czechoslovakia. Meets monthly except during July, August, and September. Annual general meeting.

Deutsche Röntgen-Gesellschaft
Secretary, Dr. med. Peter Kröker, Evangelisches Krankenhaus, Huyssens Stiftung, (22a) Essen.

Societa Italiana di Radiologia Medica
Secretary, Prof. Mario Ponzio, Ospedale Mauriziano. Torino, Italy. Meets biannually.

Nederlandse Vereniging voor Electrologie en Roentgenologie
Secretary, Dr. B. J. Rethmeier, Bornsestraat 378, Almelo, Netherlands.

Polish Society of Radiology
Secretary, Dr. Juljusz Borejko, 59 Nowogrodzka St., Warsaw, Poland.

Gdansk Section, Polish Society of Radiology
Secretary, Dr. A. Smigielska, Akademia Lekarska, Gdansk. Meets monthly last Sunday at 10:30, X-Ray Dept., Akademia Gdansk.

Wroclaw Section, Polish Society of Radiology
Secretary, Dr. R. Marciniak, Akad. Medyczna Wroclaw, 68 Curie-Sklodowska St., Wroclaw, Poland. Meets first Sunday of each month, X-Ray Department, Akademia Medyczna Wroclaw.

Societatea Romana de Radiologie si Electrologie
Secretary, Dr. Oscar Meller, Str. Banual Mărăcine, 30, S.I., Bucuresti, Roumania. Meets second Monday in every month with the exception of July and August.

All-Russian Roentgen Ray Association, Leningrad
USSR in the State Institute of Roentgenology and Radiology, 6 Roentgen St.
Secretaries, Drs. S. A. Reinberg and S. G. Simonson. Meets annually.

Scandinavian Roentgen Societies
The Scandinavian roentgen societies have formed a joint association called the Northern Association for Medical Radiology, meeting every second year in the different countries belonging to the Association.

Sociedad Espanola de Radiologia y Electrologia
Secretary, Dr. J. Martin-Crespo, Fuencarral, 7, Madrid, Spain. Meets monthly in Madrid.

Schweizerische Röntgen-Gesellschaft (Société-Suisse de Radiologie)
Secretary, Dr. Max Hopf, Effingerstrasse 47, Bern, Switzerland.

India

Indian Radiological Association
Secretary, Dr. R. F. Sethna, Navsari Building, Hornby Road, Bombay 1, India.

The list of Meetings of Radiological Societies is published in every other issue of the Journal.

THE AMERICAN RADIUM SOCIETY

PRELIMINARY PROGRAM

The following is the tentative program which has been arranged by the Program Committee under the Chairmanship of the President, Dr. Grant Beckstrand, for the Thirty-eighth Annual Meeting of the American Radium Society to be held at the Shamrock Hotel and M. D. Anderson Hospital, Houston, Texas, Monday, Tuesday and Wednesday, April 9, 10 and 11, 1956.

Sunday, April 8, 1956

Registration: 3:00–5:00 P.M.

Cocktails: Committee on Arrangements
(*Cork Club*)

Monday, April 9, 1956

Opening Session: 9:00 A.M.*–12:00* M.

Convening of the Thirty-eighth Annual Meeting.

Presidential Address. Grant Beckstrand, M.D., Long Beach, Calif.

Comparison of Dosage Distribution and Results in Carcinoma of Cervix. Ruth J. Guttman, M.D., Forest Hills, N. Y.

Correlation of Rectal and Bladder Complications with Direct Measurements in Radium Therapy of Cancer of the Cervix. Gilbert H. Fletcher, M.D., Houston, Tex.

The Anatomy of the Female Pelvis in Relation to Cancer of the Cervix. Gray H. Twombly, M.D., New York, N. Y.

The Approximation Technic in Cancer of the Cervix. Charles L. Martin, M.D., Dallas, Tex.

The Prognostic Value of End of Treatment Biopsies in Treatment of Cancer of the Cervix. Robert E. Fricke, M.D. and M. B. Dockerty, M.D., Rochester, Minn.

Afternoon Session: 1:30–4:30 P.M.

Symposium: Choice and Timing of Palliative Procedure for Advanced Breast Carcinoma.

Hormonal Therapy. Joseph H. Farrow, M.D., New York, N. Y., Moderator.

Thiotope and Chemotherapy of Breast Carcinoma. Jeanne Bateman, M.D., Washington, D.C.

Radiation Therapy: H. B. Elkins, M D., Iowa City, Ia.

Proton Irradiation of the Pitutiary Gland. John H. Lawrence, M.D., Berkeley, Calif.

Ovarian Castration. Norman Treves, M.D., New York, N. Y.

Adrenalectomy. Daneley P. Slaughter, M.D., Chicago, Ill.

Hypophysectomy. Mortimer B. Lipsett, M.D., New York, N. Y.

3:30 P.M.

End Results in Internal Mammary Chain Dissection. Jerome A. Urban, M.D., New York, N. Y.

Carcinoma of the Breast. Robert C. Hickey, M.D., Iowa City, Ia.

Dinner Session: 6:00 P.M.

Cocktails: Courtesy Radium Chemical Company (Houston Club).

The Janeway Lecture: Reflections on Malignant Lymphomas. Lloyd F. Craver, M.D., Chief of Medicine, Memorial Center, New York, N. Y.

Tuesday, April 10, 1956

Morning Session: 9:00 A.M.*–12:00* M.

The Radiation Distribution and Dose Specification in Volume Implants of Radioactive Seeds. R. J. Shalek, Ph.D., Houston, Tex.

Possible Total Dosage During Childhood by Modern Radiological Procedures. Elizabeth Focht, Associate Physicist, New York, N. Y.

Kinetic Roentgen Therapy "Convergent Beam" Clinic and Laboratory Investigation. Manuel Riebeling, M.D., Guadalajara, Jal., Mexico.

The Use of Radioactive Isotopes in the Management of Carcinoma of the Maxillary Antrum. Arthur G. James, M.D., Columbus, Ohio.

Radioiron Tracer Studies as an Index of Tolerance to Radiation. R. Kenneth Loeffler, M.D., Houston, Tex.

An Appraisal of Statistical Reports of the Result of Therapy. Harold Tivey, M.D., Houston, Tex.

Sweat Gland Carcinoma. Louisa Keasby, M.D., Los Angeles, Calif.

Afternoon Session: 1:30–4:30 P.M.

Symposium: Cancer of the Thyroid Gland. Edgar L. Frazell, M.D., New York, N. Y., Moderator.

Relation of Histologic Types to Clinical Behavior in Cancer of the Thyroid. Patrick Fitzgerald, M.D., Brooklyn, N. Y.

Evaluation of I^{131} in Conditions of Thyroid Gland. Edward J. Rall, M.D., Bethesda, Md.

Choice of Operation in the Treatment of Papillary Thyroid Cancer. Daneley P. Slaughter, M.D., Chicago, Ill.

Further Data on the Incidence of Cancer following Irradiation in Infancy for Benign Conditions. Lenore Simpson, M.D., Buffalo, N. Y.

Radiotherapy in the Treatment of Retinoblastoma. Ivor G. Williams, M.D., London, England.

Carcinoma of the Rectum. Michael R. Deddish, M.D., New York, N. Y.

Annual Banquet: 7:00 P.M. (*Emerald Room*)

Wednesday, April 11, 1956

9:00 A.M.–*12:30* P.M.

M. D. Anderson Hospital

Round Table Discussions, limited to 20 members

9:00 A.M.

Carcinoma of the Breast. Robert L. Brown, M.D., Emory University, Atlanta, Ga.

Cobalt Beam Therapy. Norman A. McCormick, M.D., Windsor, Ontario, Canada.

Intra-oral Carcinoma. Ian MacDonald, M.D., Los Angeles, Calif.

Gynecological Carcinoma. Gray H. Twombly, M.D., New York, N. Y.

Present Status of Diagnostic Methods and Therapeutic Aims of Carcinoma of the Lung. John L. Pool, M.D., New York, N. Y.

Thyroid Cancer. Edgar L. Frazell, M.D., New York, N. Y.

10:00 A.M.

Hazards of Isotopes. Herbert M. Parker, Ph. D., Richland, Wash.

Cobalt Beam Therapy. James W. Carpender, M.D., Chicago, Ill.

Carcinoma of the Breast. Joseph Farrow, M.D., New York, N. Y.

How Should Cancer of the Larynx be Treated. John V. Blady, M.D., Philadelphia, Pa.

Diagnostic and Therapeutic Problems of Malignant Lymphomas. Lloyd F. Craver, M.D., New York, N. Y.

Carcinoma of Cervix. Manuel Garcia, M.D., New Orleans, La.

11:00 A.M.

Escorted Tours of M. D. Anderson Hospital.

INSTITUTES FOR SCIENCE TEACHERS

The Special Training Division of the Oak Ridge Institute of Nuclear Studies will conduct two one-month institutes for science teachers next summer—one for secondary-school teachers, one for college and university teachers. Both summer institutes will be sponsored by the National Science Foundation.

The secondary-school institute is scheduled to be held June 11 through July 6, 1956. The institute for college and university teachers will be presented July 9 through August 3, 1956.

No formal grant of academic credit is made by ORINS for attendance at these institutes, although participants may explore the possibilities of such arrangements with individual universities.

A stipend, including dependency allowance, applicable to traveling and living expenses, will be available to a number of participants; there is no fee for enrollment in the institutes. Participating teachers, visiting lecturers, and their families will be offered housing in a dormitory-type building with arrangements for the group to be together during meals.

Selection of participants will be made from applications of science teachers at the two levels of instruction covered by the respective institutes. A letter of endorsement will be required from a responsible official of the participant's school.

Deadline for receipt of applications for the secondary-school institute is April 1, 1956. Applications for the college institute should be submitted before April 15, 1956.

Application blanks and additional information may be obtained by writing Chairman, Special Training Division, Oak Ridge Institute of Nuclear Studies, P. O. Box 117, Oak Ridge, Tennessee.

OAK RIDGE GRADUATE FELLOWSHIP PROGRAM

The Oak Ridge Institute of Nuclear Studies has recently issued a new brochure, describing its Oak Ridge Graduate Fellowship Program, which enables graduate students in the sciences to conduct their thesis research in the facilities of Oak Ridge laboratories.

Copies of the brochure and additional information may be obtained by writing the University Relations Division, Oak Ridge Institute of Nuclear Studies, P. O. Box 117, Oak Ridge, Tennessee.

COURSES IN RADIOISOTOPE TECHNIQUES

The Oak Ridge Institute of Nuclear Studies has announced a partial schedule of courses in radioisotope techniques to be offered during 1956.

The Special Training Division of ORINS regularly conducts intensive four-week courses in the basic techniques of using radioisotopes in research, designed for mature scientists who wish to become familiar with the relatively new procedures and processes which have grown out of the atomic-energy program. The 1956 basic courses are scheduled to begin on January 9, February 6, April 16, May 14, August 6, and September 3.

The ORINS Special Training Division, in cooperation with the ORINS Medical Division, will hold special advanced courses in the use of radioisotopes in hematological studies and procedures (May 14–18) and in general medical research and procedures (May 21–25). These two advanced courses are designed for medical personnel who have had previous experience in the use of radioisotopes.

ORINS will also conduct four 1956 courses in veterinary radiological health, for armed-forces veterinary officers. Starting dates for these two-week courses will be February 27, March 12, April 3, and June 4.

Dates for additional courses will be announced as they are scheduled.

Further information may be obtained by writing the Special Training Division, Oak Ridge Institute of Nuclear Studies, P. O. Box 117, Oak Ridge, Tennessee.

EIGHTH INTERNATIONAL CONGRESS OF RADIOLOGY, 1956

The Eighth International Congress of Radiology is going to take place in Mexico from July 22 to July 28, 1956. It is being organized by the Sociedad Mexicana de Radiología under the auspices of the Mexican Government and sponsored by the Ministry of Health and Public Welfare, the Ministry of Education and the National University.

The address of the headquarters of the Eighth International Congress of Radiology is Calle del Oro No. 15, Mexico 7, D. F.—Mexico.

RADIOLOGICAL SOCIETY OF NORTH AMERICA

At a recent meeting of the Radiological Society of North America, the following officers were elected for the coming year: *President*, Dr. Clarence E. Hufford, Toledo, Ohio; *President Elect*, Dr. C. Edgar Virden, Kansas City, Mo.; *1st Vice President*, Dr. James E. Lofstrom, Detroit, Mich.; *2nd Vice President*, Dr. Peter E. Russo, Oklahoma City, Okla.; *3rd Vice President*, Dr. Walter H. Ude, Minneapolis, Minn.; *Historian*, Dr. Howard P. Doub, Detroit, Mich.; *Secretary-Treasurer*, Dr. Donald S. Childs, Syracuse, N. Y.; *New Member, Board of Directors*, Dr. H. Milton Berg, Lincoln, Nebr.

BOOK REVIEWS

Books sent for review are acknowledged under: Books Received. This must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interest of our readers as space permits.

I. Studies on the Determination of Fibrinogen in Human Blood Plasma; II. Studies on the Trypsin and Plasmin Inhibitors in Human Blood Serum. The Scandinavian Journal of Clinical & Laboratory Investigation, Supplement 14. By Kjell Jacobsson. Paper. Pp. 102, with 11 figures and 14 tables. The Scandinavian Journal of Clinical & Laboratory Investigation, Medical Department A., Rikshospitalet, Oslo, Norway, 1955.

The first portion of this monograph is concerned with the description of a method for the quantitative determination of fibrinogen in plasma based on the separation of fibrin by clotting with thrombin in the absence of calcium and after syneresis; the clot is dissolved in a urea solution. Following this the optical density is determined at 279μ.

This method is a modification of Laki's work in 1942, in which thrombin was introduced as a substitute for the calcium which had been used since Kossler and Pfeiffer's efforts in 1896. It is offered as a supplement to numerous other methods of fibrinogen determination; these include the gravimetric method, nitrogen determination, colorimetric determination of fibrin, determination of turbidity of flocculated fibrin, determination of turbidity of a plasma clot, refractive index, and viscosimetric determination. The standard error of a single determination was found to be $\pm$ 1.0 per cent when determinations were made on 1 ml. samples. The average fibrinogen concentration in 130 apparently healthy persons was found to be 0.25 per cent for men and 0.27 per cent for women. Inaccuracies of the method may result from occlusion of other proteins in the fibrin clot plus the possible interference with optical density by serum of icteric patients.

In the second section of the monograph the author presents the results of detailed studies on the standardization of trypsin with soybean trypsin inhibitor. Interest in this problem dates back to the suggestion by Kunitz in 1945 that the crystalline trypsin-inhibitor derived from soybeans might be used as a standard for laboratory determination of trypsin. Subsequently, the instability of both of these substances has resulted in considerable conflict in published reports. The author finds that using casein substrate the amount of trypsin inhibited is not directly proportional to the amount of soybean trypsin inhibitor used when the original procedure is followed; it is found proportional when enzyme and inhibitor are mixed in the presence of calcium at pH 7.6 before mixing with substrate. The use of hemoglobin as a substrate is also discussed.

E. M. Knights, M.D.

Roentgenographic Technique. By Darmon Artelle Rhinehart, A.M., M.D., F.A.C.R., Emeritus Professor of Anatomy and Roentgenology, University of Arkansas; Honorary Member American Society of X-Ray Technicians; Honorary Registered X-Ray Technician; Roentgenologist to St. Vincent's Infirmary and the Missouri Pacific Hospitals, Little Rock, Ark. Fourth edition. Cloth. Price, $8.50. Pp. 454, with 216 illustrations. Lea & Febiger, 600 S. Washington Square, Philadelphia, Pennsylvania, 1954.

The new fourth edition of this text on roentgenographic technique has been brought up to date by the addition of new material and illustrations and a general revision of the previous edition. The fact that a book has reached the fourth revision bespeaks of its acceptance and general worth. This has been an excellent textbook for the instruction of beginners in radiology, both technicians and physicians, and the present edition will continue to serve this purpose well.

The general format of the book is unchanged. There are chapters on roentgen rays and roentgen-ray equipment with a good discussion of the basic physics concerned, the operating characteristics of roentgen-ray generators and the laws that govern roentgen-ray exposures. The development of a basic roentgenographic technique is given and the final section describes and illustrates the standard positions used in roentgen examinations.

This book is highly recommended as one of the best in its field. It will be particularly use-

ful as a basic text for the instruction of student technicians.

Lester W. Paul, M.D.

Histopathology of the Skin. By Walter F. Lever, M.D., Clinical Associate in Dermatology, Harvard Medical School; Assistant Dermatologist, Massachusetts General Hospital; Associate in Dermatology, Peter Bent Brigham Hospital; etc. Second edition. Cloth. Price, $12.00. Pp. 518, with 281 illustrations, 8 in color. J. B. Lippincott Company, East Washington Square, Philadelphia 5, Pennsylvania, 1954.

This second edition of a textbook of histopathology of the skin includes all of the important advances in dermopathology made during the five years since the first edition was published in 1949. These advances include the newer concepts in the differentiation of the vesicular and bullous diseases, especially of pemphigus. Note is also taken of the use of new stains such as the periodic Acid-Schiff reaction for the demonstration of fungi in tissue. The important advances in the concept of the histogenesis of the melanocyte is also given consideration in the chapter on pigmented nevi and malignant melanoma, which chapter incidentally has been completely rewritten. Fifty-six new photomicrographs have been added and fourteen old photomicrographs have been replaced by better ones.

The book as a whole is written in a very clear manner and is exceptionally well organized. It is written primarily for the dermatologist; however, it should be useful to every pathologist since dermopathology is given little consideration in the standard textbooks of pathology. The book is the most concise but still complete, best balanced and best written textbook of its kind in the English language.

Arthur C. Curtis, M D.

Radiation Biology. Volume I: High Energy Radiation. Part I and Part II. Edited by Alexander Hollaender, Director of Biology Division, Oak Ridge National Laboratory. Cloth. Price, $17.50. Pp. 1265, with numerous illustrations. McGraw-Hill Book Company, Inc., 330 West 42nd Street, New York 36, New York, 1954.

This treatise, which was prepared under the auspices of The Committee on Radiation Biology of the National Research Council, is the first of a three volume set on the subject of the interaction of radiations with biological systems. Subsequent volumes will deal with ultraviolet and visible light, while Volume I (in two parts) is concerned with high energy radiations. It is made up of chapters by eminent authorities in their respective fields and covers the subject matter in a fairly complete fashion. Part I opens with a discussion of the principles by which high energy radiations transfer energy to the medium being radiated and is followed by a chapter on measurement of ionizing radiations. The third chapter discusses the physical mechanisms responsible for chemical changes due to the transferred radiant energy. The remaining chapters of Part I discuss biochemical effects of radiations, biological aspects of linear energy transfer and genetic effects of radiations. The subject matter of Part II ranges from chromosome aberrations due to radiations through the effect of radiations on developmental, physiological and hematological processes to effects on histology and finally on carcinogenesis.

On the whole this volume should prove to be an especially valuable source book of information, theories and hypotheses for both the advanced student of radiobiology and mature investigators in any field that utilizes radiations as experimental tools as well as those directly interested in the biological effects of high energy radiations.

Leon O. Jacobson, M.D.

Grundlagen der Röntgendiagnostik und Röntgentherapie. Von Prof. Dr. G. Schulte, Recklinghausen, und Prof. Dr. F. Kuhlmann, Essen. Dritte, neu bearbeitete Auflage. Cloth. Price, DM 29.70. Pp. 298, with 267 illustrations. Georg Thieme, Herdweg 63, Stuttgart, Germany (Grune & Stratton, Inc., New York, New York), 1952.

This is the third edition of an introductory text for the students on roentgen diagnosis and radiation therapy. Like all such short textbooks, it reflects the preferences and special interests of the author. There is an introductory chapter of 23 pages on the physical-technical foundation of radiology followed by 4 pages on dosage, 4 pages on techniques of radiation therapy, ½ page on radiation damage and 1½ pages on protection. The main body of the books consists of 200 pages on roentgen diagnosis with the chapters on bones and joints (80 pages), lungs (50 pages) and gastrointestinal tract (40 pages) equally well and very adequately dealt

with. There are 263 pictures, most of them reproductions of roentgenograms with all the excellence which is expected again of books printed in Central Europe. There are many diagrams, particularly in the chapter on "Lungs" illustrating such entities as pulmonary segments, lobar and segmental pneumonias, inter-lobar effusion and others. All of them are clear and well done. The chapter on bones not only contains excellent anatomical illustrations (most of them adapted from Grashey's atlas) and roentgenograms of common bone and joint diseases, but also such rarities as marble-bone disease and melorrhostosis.

The last 28 pages are devoted to roentgen therapy and treatment with radium and radioactive substance.

The obvious shortcomings of the book are the absence of a chapter on "fluoroscopy" and the inadequate space devoted to protective measures.

The diagnostic section can be highly recommended to the German-speaking student or as an introductory text for a prospective resident in radiology.

Egon G. Wissing, M.D.

Blood Volume, Hemolysis and Regeneration of Blood in Pernicious Anemia. The Scandianvian Journal of Clinical & Laboratory Investigation, Supplement 16. By Leif Hallberg. Paper. Pp. 127, with 25 figures and 33 tables. The Scandinavian Journal of Clinical & Laboratory Investigation, Medical Department A., Rikshospitalet, Oslo, Norway, 1955.

A survey is made of various methods available for determination of total hemoglobin and the carbon monoxide method (Sjostrand's modification) is selected. Following a discussion of the relationship between hemolysis and endogenous formation of carbon monoxide, the author concludes that the concentration of COHb is a fairly good indicator of the degree of hemolysis, even with simultaneous variations of the total amount of hemoglobin. He uses a method based on COHb to study the life span of erythrocytes of pernicious anemia and further concludes that pernicious anemia should be regarded as a true hemolytic anemia, as the decrease of the circulating red cell mass is "very probably not due to a decreased production of red cells but to a decreased viability of the red cells."

The concept that pernicious anemia is a hemolytic disease is certainly not new; this view was the most prevalent one in the last century. It is generally conceded that the life span of the erythrocyte in pernicious anemia is shortened, and the great increase in excretion of urobilinogen and urobilin by patients in relapse is good evidence of increased blood destruction. However, most recent studies seem to emphasize faulty erythrocyte formation as the immediate cause of the cellular dissolution. It would appear from the evidence presented that these cells undergo a type of "auto-hemolysis." The author feels that most of the increased hemolysis is caused by cells with a life span of less than one day, referring to work of earlier investigators with radioactive iron in support of this conclusion.

E. M. Knights, M.D.

Semeiotica Neuroradiologica. By Prof. Mario Lenzi, Direttore inc. dell'Instituto di Radiologia della Università di Modena. Cloth. Pp. 320, with 400 illustrations. Cromotipia Ettore Sormani, Via Valparaiso, 3, Milano, Italy, 1954.

In this volume Professor Lenzi has collected the best information available today on neuroroentgenologic diagnosis. He has condensed it into 320 pages and illustrated it with excellent roentgenograms and schematic drawings.

The first chapter deals with the technique of the various examinations. This includes plain roentgenography, laminagraphy, encephalography, ventriculography and angiography, both arterial and venous. The indications and contraindications of the various procedures are given in a clear and sensible manner. The second chapter discusses anomalies of the skull, traumatic and inflammatory processes, intracranial calcifications, localized destruction of bone, changes in the sutures and in the sella. The third chapter describes the various signs of intracranial tumors and the fourth chapter discusses conditions which simulate the presence of intracranial neoplasms. The fifth chapter is devoted to the diagnosis of nature and to the localization of intracranial lesions. The remainder of the book is given to the spinal column and the spinal cord and contains chapters on technique, anatomy, myelography in its opaque and nonopaque forms, indications and contraindications of its various procedures. The author then describes anomalies, calcifications, bone production and destruction, curvatures of the spine and disk pathology. The

chapter on intramedullary and extramedullary tumors is particularly good and clarified by excellent drawings.

This book is clearly written, well illustrated and represents a real addition to the growing literature on neuroroentgenology.

Cesare Gianturco, M.D.

BOOKS RECEIVED

Seventh International Congress of Radiology. The Invited Papers. Acta Radiologica. Supplementum 116. Paper. Pp. 723, with numerous illustrations. Acta Radiologica, Stockholm 2, Sweden, 1954.

Proceedings of the Second National Cancer Conference. Volumes I and II. Published by American Cancer Society, Inc., National Cancer Institute of the U. S. Public Health Service and American Association for Cancer Research. Cloth. Price, $7.50 per set. Pp. 1687, with numerous illustrations. Distribution Manager, American Cancer Society, 47 Beaver Street, New York 4, New York, 1954.

Radio-Anatomie Générale de la Tête. Par Robert Aubaniac, Agrégé d'Anatomie, and Jacques Porot, Assistant d'Electro-Radiologie des Hôpitaux de Paris. Paper. Price, 5.000 fr. Pp. 152, with numerous illustrations. Masson et Cie, Editeurs, 120 boulevard Saint-Germain, Paris-6e, 1955.

Fundamentals of Radiobiology. By Z. M. Bacq, Professor in the University of Liege, Corresponding Member of the Royal Academy of Medicine of Belgium, and Peter Alexander, Chester Beatty Research Institute, Institute of Cancer Research, Royal Cancer Hospital, London. Cloth. Price, $6.50. Pp. 389, with numerous illustrations. Academic Press Inc., Publishers, 125 East 23rd Street, New York 10, New York, 1955.

Der Herzkatheterismus bei Angeborenen und erworbenen Herzfehlern. Von Prof. Dr. Otto Bayer, Oberarzt der I. Med. Klinik Düsseldorf; Dr. Franz Loogen, Assistent der I. Med. Klinik Düsseldorf, and Dr. Hans Helmuth Wolter, Assistent der I. Med. Klinik Düsseldorf. Cloth. Price $8.60. Pp. 191, with 131 illustrations. Georg Thieme Verlag, Stuttgart, Herdweg 63, Germany, 1954.

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Holt, M.D., Professor, Department of Radiology, University of Michigan; and Fred Jenner Hodges, M.D., Professor and Chairman, Department of Radiology, University of Michigan; RADIATION THERAPY edited by Harold W. Jacox, M.D., Professor of Radiology, College of Physicians and Surgeons, Columbia University; Chief, Radiation Therapy Division, Radiologic Service, Presbyterian Hospital, New York City, and Morton M. Kligerman, M.D., Associate Professor of Radiology, College of Physicians and Surgeons, Columbia University; Assistant Radiologist, Presbyterian Hospital, New York City. Cloth. Price, $9.00. Pp. 413, with 344 illustrations. The Year Book Publishers, Inc., 200 East Illinois Street, Chicago, Illinois, 1955.

THE YEAR BOOK OF RADIOLOGY (1955–1956 Series). RADIOLOGIC DIAGNOSIS edited by John Floyd Holt, M.D., Professor, Department of Radiology, University of Michigan; and Fred Jenner Hodges, M.D., Professor and Chairman, Department of Radiology, University of Michigan; RADIATION THERAPY edited by Harold W. Jacox, M.D., Professor of Radiology, College of Physicians and Surgeons, Columbia University; Chief, Radiation Therapy Division, Radiologic Service, Presbyterian Hospital, New York City; and Morton M. Kligerman, M.D., Associate Professor of Radiology, College of Physicians and Surgeons, Columbia University; Assistant Radiologist, Presbyterian Hospital, New York City. Cloth. Price, $9.00. Pp. 413, with 344 illustrations. The Year Book Publishers, Inc., 200 East Illinois Street, Chicago, Illinois, 1955.

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PRIMEIROS ENSAIOS DE RADIOTERAPIA MICROLOCALIZADA DA HIPÓFISE E DO HIPOTÁLAMO. Pelo Prof. Dr. Carlos Santos, Da Faculdade de Medicina de Lisboa. Paper. Pp. 69, with 19 illustrations. Author's address, Av. da Liberdade (11) Lisboa, Portugal, 1953.

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ROENTGENOGRAPHIC TECHNIQUE. By Darmon Artelle Rhinehart, A.M., M.D., F.A.C.R., Emeritus Professor of Anatomy and Roentgenology, University of Arkansas; Honorary Member American Society of X-Ray Technicians; Honorary Registered X-Ray Technician; Roentgenologist to St. Vincent's Infirmary and the Missouri Pacific Hospitals, Little Rock, Ark. Fourth edition. Cloth. Price, $8.50. Pp. 454, with 216 illustrations. Lea & Febiger, 600 S. Washington Square, Philadelphia, Pennsylvania, 1954.

Vol. 75, No. 3

ABSTRACTS OF RADIOLOGICAL LITERATURE

Department Editor: T. Leucutia, M.D., Harper Hospital, Detroit 1, Michigan

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ROENTGEN DIAGNOSIS

Head

Thomson, J. L. G. Enlargement of the sella turcica; a report on 27 cases. *Brit. J. Radiol.*, Sept., 1955, *28*, 454–461. (From: The Churchill Hospital, Oxford, England.)

The author presents 27 cases of enlargement of the sella turcica from various causes to prove that roentgenologic differentiation between intrasellar, extrasellar, and remote lesions on the basis of the appearance of the sella is not valid. Numerous intracerebral abnormalities are capable of producing sellar enlargement so that evaluation of the underlying etiology requires clinical investigation and air and arteriographic roentgen studies to localize the cause of the enlargement.

In the series of cases reported, intrasellar lesions which caused sellar changes were: pituitary adenomas, carcinoma of the pituitary, and craniopharyngioma; suprasellar meningioma and astrocytoma, chordoma, ependymoma, gliomatosis, plasmocytoma, aneurysm, and syphilitic meningitis; while remote lesions were aqueduct stenosis, pontine and cerebellar tumors, and parietal meningiomas.

Four features which were constant were ballooning of the sella and evaluation of the anterior clinoid processes with intrasellar tumors, foreshortening of the dorsum sellae with suprasellar tumors, and depression of the anterior clinoids with suprasellar tumors. The sellar changes and their causes are illustrated by roentgenographic reproductions and diagrams.—*Sue L. Nickey, M.D.*

Ott, P., and Rosteck, K. Kontaktaufnahmen mit Nahstrahlröhren am Schädel. (Contact-short distance roentgenography of the skull.) *Fortschr. a. d. Geb. d. Röntgenstrahlen ver. m. Röntgenpraxis*, Sept., 1955, *83*, 401–408. (From: Röntgen-Radium-Abteilung der Städt. Krankenanstalten, Mannheim, Germany.)

A cleaner or less obstructed view of the zygomatic arch can be obtained by the use of a van der Plaats' or contact tube, where the focal skin distance is 38 mm. and to which has been added enough filtration to reduce the exposure to the skin from 90 r to 30 r. The end of the tube is placed on the opposite tuberculum articulare perpendicular to the German baseline but with a 10° upward tilt. The cassette is placed against the involved side so that the central ray is perpendicular to its plane at its center. Exposures in the conventional axial views are also made for a complete evaluation.

For roentgenograms of the atlanto-occipital joints by this method, the patient is seated or lying supine with the chin as close to the chest as possible. The end of the tube is placed over the glabella so that the central ray passes through the joint. Both eyes must be protected by lead or lead-rubber disks.

This method is also helpful in localizing indistinct fractures of the cranial vault. The tube is pointed over the suspicious area and exposures are made from each side of the head. The physical factors are 44 kv., 2 ma., 4–8 seconds.—*J. Zausner, M.D.*

Sherman, Robert S., and Chu, Florence C. H. Carcinomatous invasion of the jaw bones roentgenographically considered. *Radiology*, Oct., 1955, *65*, 581–586. (Address: Dr. Sherman, 444 East 68th St., New York 21, N. Y.)

Invasion of the jaw bone by continuity from neoplasms originating in the gums, antrum, hard palate, floor of the mouth, tonsil, nasal cavity, buccal mucosa, tongue, soft palate, lip, salivary glands and from a nearby lymph node is described. Of the above, cancer of the gum most frequently invades the adjacent bones.

In order to better find and visualize areas of involvement, careful technique with exposure in many views of the jaw bones is necessary. The basic or minimum routine for cancer of the various anatomic sites is described. Sixty-one cases of proven jaw bone involvement have been studied by the authors and are the basis for this report.

The most important roentgenographic features of bony invasion are as follows: The bone destruction occurs most commonly at the alveolus and usually is apparent as a V-shaped area of erosion, which is rather characteristic. The edges may be either distinct, ill-defined, or at times slightly ragged. There is usually no internal pattern except for the occasional presence of a few tiny bone fragments. There is no bone production and seldom any periosteal reaction is evident. A soft tissue mass may be seen in cases of carcinoma of the antrum, but rarely can be identified in other situations. Teeth, if present within the tumor area, usually exhibit destruction of the lamina dura.

The differential diagnosis must include osteomyelitis and occasionally, in post-irradiated cases, the possibility of radiation osteitis. Osteomyelitis usually shows a patchy bone destruction in the medullary part of the bone, diffuse in distribution, often associated with some degree of sclerosis and occasionally sequestration and periosteal reaction. Early radiation osteitis, before infection sets in, is manifest by a slight degree of irregular diffuse bone sclerosis with faint cortical irregularity and shagginess. The advanced cases usually have infection also present in which event the picture resembles an osteomyelitic process. Other more rare entities to be ruled out include the lytic type of osteogenic sarcoma, epulis, and a blood-borne metastatic deposit.—*Donald N. Dysart, M.D.*

Neck and Chest

Lindskog, Gustaf E., and Spear, Harold C. Middle-lobe syndrome. *New England J. Med.*, Sept. 22, 1955, *253*, 489–495. (From: Department of Surgery, Yale University School of Medicine, and Grace-New Haven Community Hospital, New Haven, Conn.)

Atelectasis with chronic pneumonitis involving the right middle lobe has received considerable attention recently. Any inflammatory process leading to lobar hilar lymphadenopathy may result in bronchostenosis, with consequent atelectasis and pneumonitis. The right middle lobe is particularly susceptible because its lobar bronchus is surrounded by a cluster of lymph nodes. In addition the small caliber of this bronchus and its emergence at almost a right angle from the intermediate bronchus hamper adequate drainage.

The authors have selected seven case reports to illustrate that there is a wide variety of middle lobe lesions, which cannot always be differentiated with certainty except by operative interference and pathological study. The lesions in this series include nonspecific atelectasis and chronic pneumonitis, with secondary bronchiectasis; bronchogenic carcinoma; atelectasis with organizing pneumonitis secondary to tuberculous hilar lymphadenopathy; parenchymal tuberculosis; chronic abscess, with organizing pneumonitis; acute pneumonitis with resolution; and lipoid pneumonia secondary to ingestion of a mineral oil preparation over a period of many years.—*Arthur E. Childe, M.D.*

Joynt, G. H. C., and Harnick, L. R. Bronchography with dionosil. *Surg., Gynec. & Obst.*, Oct., 1955, *101*, 425–430. (From: Toronto Hospital and University of Toronto Medical School, Toronto, Canada.)

Dionosil, a new contrast medium for bronchography, is available in two forms: (1) an aqueous suspension and (2) a suspension in oil. In these preparations, the iodine is in organic combination and there is no breakdown of free or inorganic iodine responsible for the untoward reactions seen in other contrast media. The clinical section of this report does not include any experience with "dionosil oily" which is slightly less irritating to the bronchial mucous membrane but has the disadvantage of an oily base, namely a tissue reaction characterized by granulation formation.

The greatest advantage of dionosil is its rapid elimination from the lungs in three to four days so that plain roentgenograms are not obscured. The urinary excretion rate in rabbits, carried out by labeling the compound with I^{131}, after oral or intratracheal administration showed a minimum of 95 per cent recovery in seventy-two hours.

It is well tolerated by patients and is relatively nontoxic. Occasionally there is a febrile reaction for twenty-four to forty-eight hours but it has been used in active pulmonary tuberculosis without untoward incident. The medium coats the mucosa of the bronchial tree and does not produce alveolar filling. Since 1952, over 900 bronchographies have been carried out with aqueous dionosil at the Toronto Western Hospital.

In addition an experimental study of dionosil and lipiodol bronchography has been done on dogs. Instillation was performed under fluoroscopy, films taken, the dogs sacrificed at varying intervals, and the lungs studied grossly and microscopically. With aqueous dionosil no granulomatous reaction was noted. Both "dionosil oily" and lipiodol produced granulomas in some of the dogs in which they were used.—*William C. MacCarty, Jr., M.D.*

Wilson, John W. Diagnosis of infrapulmonary pleural effusion. *J.A.M.A.*, Aug. 20, 1955, *158*, 1423–1427. (Address: 5201 Harry Hines Blvd., Dallas, Texas.)

Infrapulmonary effusion may be defined as a collection of any liquid or fluid in the pleural space beneath the lung and above the diaphragm. It resembles an elevated diaphragm and has been described as "rare;" however, it is encountered rather frequently. Traumatic hemothorax is one of the many etiologies of this condition.

Twenty-four cases make up the basis of this article and the etiology of the infrapulmonary pleural effusion is divided as follows: pulmonary infarction, 2 cases; trauma with hemothorax, 6 cases; acute rheumatic heart disease, 2 cases; Hodgkin's disease, 2 cases; and 1 case each of empyema, basilar pleurisy, breast carcinoma with pleural metastases, bronchogenic carcinoma, chronic glomerulonephiritis, sicklemia, and dissecting aneurysm of the aorta. There were 5 cases of arteriosclerotic and/or hypertensive heart disease with failure. Mechanism for the confinement of effusions in the subpulmonic space is not known. It would appear, however, that there are two basic principles in the mechanism of infrapulmonary fluid collection. The base of the lung is more elastic than the remaining portions and is therefore more mobile. In addition the negative infrapleural pressure is greatest at the base as a result of diaphragmatic movement and the resultant tendency is for the fluid or liquid to be sucked into the infrapulmonary space.

Any patient who shows clinical or roentgenographic signs simulating an elevated diaphragm should have further studies to exclude the presence of infrapulmonary effusion. It may represent the earliest stages of fluid collected in the pleural cavity. The common diagnostic roentgen features of pleural effusion may be completely absent.

Fluoroscopic or roentgenographic examinations of the patient in different postures so that the shift of

effusion from the infrapulmonary space can be observed is perhaps the easiest and most informative of the roentgen procedures. Lateral decubitus films are of particular value. With the patient in Trendelenburg position the effusion gravitates over the apex. With any of these positions the effusion is distributed to dependent portions of the pleural cavity and the illusion of an elevated diaphragm is dispelled.

In infrapulmonary effusions the respiratory incapacity may be quite severe even though the volumetric accumulation of fluid is relatively small. Thoracentesis is recommended if there are any symptoms of respiratory embarrassment.—*William C. MacCarty, Jr., M.D.*

Higgins, John A., Juergens, John L., Bruwer, André J., and Parkin, Thomas W. Loculated interlobar pleural effusion due to congestive heart failure. *A.M.A. Arch. Int. Med.*, Aug., 1955, *96*, 180–187. (From: Mayo Clinic and Mayo Foundation, Rochester, Minn.)

Loculated interlobar pleural effusions due to congestive heart failure have been called "vanishing tumors" of the lung. They can be of various shapes and sizes and the criteria for their diagnosis are (1) the appearance of a circumscribed interlobar density concomitantly with the signs or symptoms of congestive heart failure and (2) the disappearance of this shadow after successful treatment of the cardiac decompensation.

Over a ten year period 5 cases at the Mayo Clinic satisfied these criteria and are reported briefly. There are in addition another 36 well documented cases in the literature bringing the total to 41. In 63.4 per cent of these the effusions were located in the right transverse fissure alone and in 14.6 per cent in the right transverse and the right oblique fissures; thus the transverse fissure was involved in 78 per cent of the cases. One of the reasons for this preponderance may be that loculated effusions at this site are more readily discovered on the routine roentgenograms showing posteroanterior views of the thorax, since the rays pass through the greatest diameter of the mass in the effusion. Effusions in the oblique fissure on either side are best seen on lateral views. The average age of the patients was 55.2 years.

A loculated interlobar effusion occurs when obliterative pleuritis makes the remainder of the pleural space unavailable for the accumulation of fluid. This is not always the case, however, and only rarely do these patients give a history of pleurisy.

Of the 5 Mayo Clinic cases, 2 were referred to the Clinic because of possible tumors of the lung and in another case a diagnostic biopsy was considered. The possibility of a circumscribed density in the lung being due to interlobar effusion with congestive heart failure should always be kept in mind.—*William C. MacCarty, Jr., M.D.*

Abdomen

Smithers, D. W. The association of cancer of the stomach and oesophagus with herniation of the oesophageal hiatus of the diaphragm. *Brit. J. Radiol.*, Oct., 1955, *28*, 554–564. (From: Royal Marsden Hospital and Institute of Cancer Research, Royal Cancer Hospital, London, S.W.3, England.)

This is the third paper in a series dealing with hiatus hernia, short esophagus, partial thoracic stomach and their association with peptic ulceration and cancer. The author believes that the association of malignant disease of the stomach and esophagus is more common than published reports would indicate. He summarizes 96 cases collected from the literature and 12 new cases; 41 cases had cancer of the esophagus, 41 cancer at the cardia and 26 cancer of the stomach. In the author's 12 cases, 11 had primary tumor of the esophagus and one had a tumor of the stomach. In another group of 1,102 patients with hiatus hernia reported on by various authors, 40 patients had cancer of the stomach or esophagus. Most of the tumors are adenocarcinomas arising at or close to the cardia.

Reflux esophagitis which commonly follows sliding hiatal herniation might predispose to the formation of malignant tumors of the esophagus. Other factors which the author feels are more important are the fact that a small lower portion of the esophagus is frequently lined by glandular epithelium which, at this constricted site is particularly liable to malignant disease, and that there is preferential spread into the submucous lymphatics of the esophagus by tumors arising at the cardia. Such tumors cause dilatation of the hiatus and produce irritation, both of which predispose to herniation.—*Arthur B. Smith, M.D.*

Piatt, Arnold D., and Erhard, Gerald A. Lesions with chronic symptoms producing pyloric obstruction and gastric decompensation. *Radiology*, Oct., 1955, *65*, 503–517. (Address: Dr. Piatt, 36 West Locust St., Newark, Ohio.)

The occasional finding on roentgen examination of the upper gastrointestinal tract of a tremendous dilatation of the stomach with pronounced retention of gastric fluids due to obstruction at the pyloric end of the stomach plus the history of chronic symptoms raises the question as to what pathologic process produces this phenomenon. A review of the literature revealed conflicting opinions regarding this problem. Among the entities producing this picture are listed: pyloric ulcer, carcinoma of the pylorus, pyloroduodenal ulcer or inflammation, duodenal ulcer, duodenal stenosis, adhesions, syphillis, hypertrophic pyloric stenosis, benign pylorospasm, extrinsic pres-

sure, pedunculated benign or malignant tumors near the pyloric valve, foreign bodies, congenital duodenal atresia, and congenitally enlarged mucosal folds of the pylorus.

The authors present their series of 18 cases which showed practically identical findings of pyloric obstruction and a greatly dilated atonic stomach, with gastric retention at 6 and 24 hours. In 12 of their cases a benign peptic ulcer was established definitely as the cause of their findings. In two more, the findings were probably due to ulcer changes, but a co-existing adenocarcinoma was present in one, and in the other progressive roentgen changes were observed before death. Benign pyloric hypertrophy was found in another, while the other three were found to have malignancy—one proved extragastric and others with unknown primary location.

From this study the authors conclude that benign peptic ulcers are the predominant lesions producing chronic pyloric obstruction with consequent gastric decompensation. Other possibilities, however, as mentioned above which can duplicate the clinical and roentgen picture, cannot be excluded.—*Donald N. Dysart, M.D.*

Culver, Gordon J., Bean, Berten C., and Berens, David L. Gastric lymphoma. *Radiology*, Oct., 1955, *65*, 518–529. (From: Department of Radiology, Buffalo General Hospital, Buffalo, N. Y.)

Numerous reports of the various types of gastric lymphoma have appeared in the literature, but no detailed analysis of the entire group has been published, nor has the similarity of gross pathologic changes in the various conditions been emphasized. A review of this subject is therefore presented, and 9 illustrative cases are reported.

According to the authors, the lymphomas account for less than 2 per cent of the malignant gastric lesions. A definite etiologic factor has not been established, though numerous theories have been advanced. The condition has been held to be either an atypical form of tuberculosis, a specific infection by an unknown pathogenic micro-organism, a granuloma, a neoplastic disease, or a lesion due to unknown etiology.

Grossly three forms of gastric lymphomas may be described, these being ulcerative, tumor-like, and diffuse. The gross pathologic appearance and certain aspects of the microscopic picture are discussed since they explain some of the alterations in physiology observed by the roentgenologist. The roentgenologic features which characterize these lymphomas are described in reference to the types of gastric wall involvement encountered. It is also pointed out that peristalsis may be present throughout the lesion despite massive involvement, and that a careful search may show that the pyloric valve has been crossed. Other abdominal findings such as displacement of the stomach or enlargement of the liver and spleen may be of further aid in accurate diagnosis.

Differential diagnosis may be impossible, since clinical symptoms and signs and roentgenologic findings are often not diagnostic. Gastric carcinoma, gastritis, syphilis, tuberculosis, leiomyosarcoma, amyloid and lipoid infiltration must all be considered when roentgenologic findings suggestive of gastric lymphoma are visualized. Appreciation of the gross changes commonly encountered, careful examination, and utilization of gastroscopy in all suspicious cases will, however, often result in accurate preoperative diagnosis.—*A. Ralph Watson, M.D.*

Adler, Denis C., Jacobson, George, Heitmann, Kenneth A., and Watson, Derrell D. Insulin-induced hypermotility in the roentgen examination of the stomach and duodenum. *Radiology*, Oct., 1955, *65*, 530–538. (Address: Dr. Jacobson, 1200 N. State St., Los Angeles 33, Calif.)

The induction of active peristalsis in the stomach and duodenum by injection of various pharmacologic agents has been studied by various investigators. Morphine, physostigmine, a combination of morphine and physostigmine, atropine, ipecac, and insulin have all been used with variable effects on the stomach and duodenum and differing opinions on their value.

In view of the seemingly better results using insulin, the authors studied a series of patients in whom roentgen examination of the stomach and duodenum was done about 5 minutes after intravenous administration of 0.2 units of crystalline insulin per kilogram body weight. This series consisted of 56 patients in whom the findings in the first stomach examination had been inconclusive. The results of the re-examination following insulin were classified as to whether they were of definite value, of questionable value, or of no value.

In slightly less than one-half of the cases the procedure was considered of definite value, while in one-fourth it was of questionable value, and in the remainder it was of no value. In certain selected cases of questionable antral deformities, gastric ulcer, duodenal ulcer, and deformities of the duodenal bulb or second portion of the duodenum, the insulin re-examination was considered of definite value. In general a question of a gastric neoplasm or of a lesion in the upper third of the stomach could not be settled with this procedure.

In conclusion, the authors feel that due to the variability of response to insulin it is doubtful that the information gained was more than might be expected from any other re-examination.—*Donald N. Dysart, M.D.*

Lust, Franz J. Roentgenological findings in gastric and duodenal ulcers in children. *Am.*

J. Digest. Dis., July, 1955, *22*, 189–194. (From: Department of Radiology, Bellevue Hospital Center, New York, N. Y.)

In the past twenty years only 20 cases of gastric ulcers in children have been reported in the literature. It has been the author's experience, that routine roentgenologic examination of the gastrointestinal tract of children has been unsatisfactory. Another point is, apparently, the prevalent idea that ulcerating lesions of the upper gastrointestinal tract are rarities. Frequently, only after bleeding has taken place, have roentgenologic studies been advised. Even known ulcers in adults, in the first four weeks after bleeding, are extremely difficult to demonstrate. This clinical-roentgenologic experience should be taken into consideration.

The author overcomes the difficulty in children by using a new method of examination. He discusses the superiority of roentgenography over fluoroscopy, reducing the latter to a secondary position. He also advocates the use of a shielded screen (Belloscope) for use in normal light. This feature of the examination, and the emphasis on removing any mental stress of the children, apparently, permitted a greater accuracy in diagnostic procedure. He emphasizes the use of repeated spot-films.

The second difficulty is due to the extremely rapid transit of the contrast substance through the duodenum in children. The lesions are so shallow that they can only be recognized after studying many exposures.

The incidence of pathology is high when these thorough methods are used.

The roentgenologic signs of ulcers in children are the same as those seen in acute ulcers in adults. In children, fibrosis has not set in, hence the clinical experience of frequent perforations. The gastric ulcer shows a niche. Niches on the greater curvature have not been described as yet. Most of the ulcers are on the distal half of the lesser curvature or in the region of the gastric antrum.

The diagnosis of an ulcer of the duodenum depends, too, on the demonstration of a niche. In several cases, the niche seems to be in the second portion of the duodenum. In some cases, a very deformed duodenal bulb was visualized.

The functional pathology in these cases is of importance. The studies of gastric secretion are important, for they reveal, without the use of a stomach tube, that a gastric hypersecretion is present. The second functional pathology is that of a delayed gastric emptying. The author emphasizes the study of films six hours after ingestion of the contrast suspension. If a large gastric retention is demonstrated, these little patients complain of discomfort hours after meals. This is not due to an organic stenosis, which is ruled out by studies of the stomach and duodenum.

Due to the small size of the pathological process, fluoroscopy usually fails to show the lesion. Besides, the motility of the alimentary tract is so rapid that the fluoroscopist cannot detect the lesions. Therefore, several roentgenograms and multiple spot-films are necessary.—*Stephen N. Tager, M.D.*

Freedman, Eugene, Rabwin, Marcus H., and Sava, Marcella. Benign and malignant tumors of the duodenum. *Radiology*, Oct., 1955, *65*, 557–568. (From: Departments of Radiology and Surgery, Cedars of Lebanon Hospital, Los Angeles, Calif.)

The authors report 5 cases of carcinoma of the duodenum and 3 cases of benign duodenal tumors, all surgically proved, and discuss the roentgenologic features in these cases.

Roentgen studies offer the only reliable basis for the diagnosis of duodenal tumors. The findings vary with the character, location, and extent of the tumor, but basically the same criteria apply as in the roentgen diagnosis of lesions elsewhere in the intestinal tract. The typical benign tumor presents a well-defined, regular filling defect, usually circular, within the barium-filled duodenum. Mucosal surfaces may be distorted or ulcerated, but are not destroyed. The presence of a pedicle favors a benign lesion.

An irregular alteration and subsequent disappearance of the normal mucosal pattern is present in duodenal carcinoma. When the mucosa becomes eroded, an irregular crater develops. The duodenal wall adjacent to the ulceration is thickened and fixed. The scirrhous type usually produces concentric and symmetrical constriction. In some instances, when destruction of the muscularis leads to localized weakness of the duodenal wall, the lumen may become dilated rather than narrowed. The duodenal curve does not become widened as a result of intrinsic duodenal tumor.

Carcinoma of the head of the pancreas usually exerts pressure from without. This causes spreading and enlarging of the duodenal loop. The inverted figure-of-3 sign may be found in tumor or inflammatory swelling of the head of the pancreas or the ampulla, but is not seen with duodenal cancer. Early carcinoma of the ampulla of Vater produces a localized defect on the medial wall of the second portion of the duodenum. In this stage, it is indistinguishable from early periampular duodenal cancer. Annular pancreas is a developmental anomaly and is therefore encountered most frequently in young persons. It produces a concentric regular narrowing, without ulceration. When this abnormality is encountered in adults there may be considerable dilatation of the duodenum proximal to the constriction. Chronic duodenal ulcer in a postbulbar location poses a difficult problem of differentiation. Some help in differentiation in derived from re-check examinations which usually show healing as a result of medical management.—*A. W. Sommer, M.D.*

Beranbaum, S. L., and Subbarao, Kakarla. The normal ileo-cecal valve. *Am. J. Digest. Dis.*, Sept., 1955, *22*, 254–261. (From: University Hospital, New York University, Bellevue Medical Center, New York, N. Y.)

With numerous illustrations, the authors correlate the findings of the normal ileocecal valve. Studies were made on the normal living by barium enemas and barium meals and on autopsy specimens. Great variation in the location of insertion of the ileocecal valve into the cecum was noted. The thickness of the lips was found to vary greatly from person to person and examination to examination. Anything above 6 mm. was felt to represent a hypertrophied lip on a completely filled colon. To best determine normalcy, compression film studies with the valve in profile and barium enema contrast studies should be done. In more difficult cases, studies following barium meal gave valuable additional help.—*George A. Miller, M.D.*

Madell, Samuel H., and Golden, Ross. The ileum following colectomy. *Radiology*, Oct., 1955, *65*, 539–548. (Address: Dr. Madell, 622 West 168th St., New York 32, N. Y.)

Since there have been conflicting reports concerning dilatation of the ileum following colectomy, the authors present results of roentgen studies of the ileum at various intervals after surgical procedures in which all or a large part of the large bowel was removed.

Eighteen patients were examined, of whom 10 had ileostomy, 4 ileosigmoidostomy, 2 ileoproctostomy, 1 ileo-anal anastomosis, and 1 sigmoidocecostomy.

On the basis of roentgen examinations, the patients fell into four groups, as follows:

1. Those with no demonstrable abnormality of the ileum.
2. Those with dilatation associated with inflammatory disease of the ileum.
3. Those with dilatation associated with constriction or stenosis at or distal to the anastomosis.
4. Two cases of dilatation of the ileum without obvious cause.

This study disclosed nothing to support the idea that enlargement of the small intestine following colectomy occurs as a physiologic compensation for the loss of the colon. Enlargement of the ileum under these conditions is regarded as abnormal. While no adequate explanation of the dilatation of the ileum in the group 4 cases was found, it is suggested that this may be the result of temporary derangement of motor physiology, the origin of which is not apparent.—*A. Ralph Watson, M.D.*

Heilbrun, Norman, and Bernstein, Charles. Roentgen abnormalities of the large and small intestine associated with prolonged cathartic ingestion. *Radiology*, Oct., 1955, *65*, 549–556. (Address: Dr. Heilbrun, 685 Delaware Ave., Buffalo 9, N. Y.)

The roentgen abnormalities previously described and accepted as associated with prolonged cathartic ingestion are narrowing and diminished haustrations in the left colon with atonicity of the transverse and right colon segments or hypotonicity of the entire colon. In 1943 marked enterocolitis-like changes were reported in a patient who had ingested irritant cathartics daily for twenty-six years. The clinical and roentgen findings in 9 patients with a history of ingestion of irritant cathartics for at least fifteen years are described in the present report. In this series the early changes were in the cecum and ileocecal valve, with extension proximally to involve the terminal ileum and distally to involve the colon as far as the sigmoid when the changes were more severe and diffuse.

Roentgen findings in the mildest cases were a foreshortened and conical cecum and shortened and gaping lips of the ileocecal valve. In the more severe cases the colon distal to the cecum was tubular with diminished haustrations. The ileum was narrowed and tubular with loss of the normal mucosal markings. Clinically, there was absence of diarrhea, cramps and bloody bowel movements with essentially negative physical and proctoscopic examinations. These are important points in the differentiation of this condition from the inflammatory lesions which its roentgen findings simulate.—*Harold C. Hamilton, M.D.*

Gianturco, Cesare, and Miller, George A. Barium in hydrogen peroxide in esophageal and gastric diagnosis. *Radiology*, Oct., 1955, *65*, 569–571. (From: Carle Hospital Clinic, Urbana, Ill.)

Barium in hydrogen peroxide is the first "pathology-sensitive" opaque agent to be developed for roentgenological diagnosis. This suspension foams in contact with ulcerated surfaces in the esophagus or stomach. Foaming or bubbling, if it occurs, is seen in twenty to thirty seconds after ingestion and is best detected fluoroscopically.

Probably the best indication for the use of this agent is the clinical suspicion of ulcerations of the lower esophagus and of neoplasms of the cardiac portion of the stomach. It is probably of little value in small intestinal diagnosis. Abundant foam develops in the presence of intragastric blood and pus, while in the absence of free blood or pus the foam is proportional to the size of the ulcerated surfaces. Retained food will also cause bubbling of the mixture. Slight effervescence occurs in normal stomachs and is of no diagnostic significance. The mixture is not palatable and, in quantities greater than 2 oz., may cause nausea and vomiting, but this amount is well tolerated if given following 2 oz. of ordinary barium in water.—*Harold C. Hamilton, M.D.*

Bischoff, Martin E., and Stampfli, Wendell P. Meckel's diverticulum; with emphasis on the roentgen diagnosis. *Radiology*, Oct., 1955, *65*, 572–577. (From: Department of Radiology, St. Luke's Hospital, Denver, Colo.)

The authors report two cases of Meckel's diverticulum which were diagnosed by preoperative roentgen studies, adding to the 33 similar cases reported previously in the literature. Emphasis in this discussion is placed on the roentgen diagnosis.

The helpful roentgen signs consist of a barium-filled diverticulum, a gas-filled diverticulum, and the presence of a calculus or opacified material within an air pocket—all located in the region of this distal portion of the ileum.

A folded-ribbon-like shadow, representing the calculus within the gas bubble, as seen in one of their cases, is suggested as being a characteristic finding when present.—*Donald N. Dysart, M.D.*

Keats, Theodore E., and Whitrock, Robert M. The application of silicones to roentgenology of the colon: a pilot study. *Radiology*, Oct., 1955, *65*, 578–580. (From: Departments of Radiology and Surgery, University of California School of Medicine, San Francisco 22, Calif.)

The results of a pilot study utilizing suspensions of barium, water, and silicone of 200 centistokes viscosity as a medium for roentgen examination of the colon are presented.

Barium enema and pneumocolon studies were performed in the isolated colon of a dog with suspensions of barium-water-silicone 50 per cent and barium-water-carboxymethylcellulose 5 per cent. Both were found to be satisfactory and no superiority of one medium over the other was demonstrated. Barium-water-silicone 10 per cent suspension was then used in 28 barium enemas in man, including 4 pneumocolons, and the results obtained were compared with a similar group of examinations using barium-water-carboxymethylcellulose 5 per cent suspension. No significant advantage of one medium over the other was demonstrated although distribution and mucosal adherence of the barium appeared to be somewhat superior with the carboxymethylcellulose suspension. —*Harold C. Hamilton, M.D.*

Link, Alexander J., Parida, Raj K., Heydemann, Julius, and Kark, Robert M. Visualization of biliary ducts by intravenous injection of new contrast medium. *J.A.M.A.*, Aug. 27, 1955, *158*, 1491–1494. (From: Departments of Radiology and Medicine, Research and Educational Hospitals, University of Illinois College of Medicine, Chicago, Ill.)

This article reports studies of 21 patients, with or without hepatobiliary disease, in whom intravenous cholangiographic examinations were done using sodium iodipamide (cholografin) as the contrast material. Prior to the examination, liver function studies were performed and 48 hours after the injection the studies were repeated. A third series was done one week later. In each case, an injection of 1 cc. intravenously was made as a sensitivity test and 40 cc. of the compound was injected after a period of five minutes. The injection was performed slowly requiring 8 to 10 minutes and no serious reactions to the intravenous infusion were encountered. One-half of the patients experienced no side effects while the other half had sensations of warmth, nausea, metallic taste or peculiar smell, dizziness, or pain in the arm and shoulders during the injection. It appears that the magnitude of the side effects was a function of the rate of injection. Roentgenograms were exposed immediately, 10 minutes, 20 minutes, 30 minutes and 60 minutes after the solution was injected. It is stated that 20 cc. of cholografin is sufficient for visualization of the gallbladder, but in these instances, visualization of the biliary ducts was under study and 40 cc. of the contrast material was elected for this purpose.

Three control patients were used and each showed good visualization of the biliary ducts within 10 to 30 minutes. Of five patients who had signs and symptoms of hepatobiliary disease, four demonstrated duct visualization. The fifth patient whose ducts were not seen had biliary cirrhosis. In the remaining 13 patients, cholecystectomy had been performed and each presented a postcholecystectomy syndrome. Of this group, five demonstrated poor or no visualization of the ducts and eight good visualization.

Liver function tests were demonstrably abnormal prior to this examination in eleven patients. Of these eleven patients, six demonstrated good visualization of the biliary ducts. On liver function tests performed after the injection, no changes were noted by serial tests of liver function.

In the six patients in whom visualization of the bile ducts was not obtained, two had free air in the ducts incident to previous surgery and four had abnormal liver function, cirrhosis, or a draining T-tube in the common duct.

From these studies, the authors conclude that indications for intravenous cholangiography are (1) complaints following cholecystectomy, (2) suspected common duct stone, (3) normal cholecystogram by other methods but persistent symptoms, (4) inability to take or intolerance to oral preparations, (5) need for rapid diagnosis.—*B. J. Parnell, M.D.*

Genitourinary System

Roth, Russell B., Kaminsky, Anthony F., and Hess, Elmer. A bacteriocidal additive for pyelographic media. *J. Urol.*, Oct., 1955, *74*, 563–566. (Address: Dr. Roth, 8 E. 12th St., Erie, Penna.)

One of the limitations of retrograde pyelography is the presence of urinary tract infection. It has been well known for a long time that catheterization of an obstructive kidney may lead to severe complications. In an attempt to overcome this difficulty the authors have investigated a number of antibiotic drugs so that the procedure of retrograde pyelography might be carried out with less danger of a closed infection of the kidney.

The drug of choice was found to be neomycin sulfate. In a 2½ per cent solution this drug is nontoxic and nonirritative and does not interfere with the density of the pyelographic needle. It is chemically compatible with a solution of skiodan and it has a satisfactory bactericidal activity. Five grams of the crystalline drug are dissolved in 100 cc. of a 40 per cent solution of skiodan. This is kept in sterile stock bottles. When ready to use, equal parts of this solution of neomycin and skiodan are mixed with plain skiodan solution so that a 2½ per cent neomycin-skiodan solution results.

Pyelographic studies made on 219 occasions using a 2½ per cent solution of neomycin sulfate in skiodan have produced no untoward reaction and the addition of this antibiotic drug is now a routine procedure in the authors' practice.—*George W. Chamberlin, M.D.*

Skeletal System

van Buchem, F. S. P., Hadders, H. N., and Ubbens, R. An uncommon familial systemic disease of the skeleton: Hyperostosis corticalis generalisata familiaris. *Acta radiol.*, Aug., 1955, *44*, 109–120. (From: Department of Medicine, Pathology Laboratory, and Roentgen Institute of The University Clinic, Groningen, The Netherlands.)

The authors report cases of a middle aged twin brother and sister with a peculiar systemic disease of the skeleton which does not fit into any classification so far described. Both showed thickened and sclerotic skull caps and enlarged and sclerotic mandibles. There was also extensive involvement of the bones of the extremeities, the clavicles and the ribs consisting of marked hyperplasia of the corticalis with extensive osteophyte formation. The size of the bones was increased and the marrow cavity reduced. Cortical thickening was chiefly localized to the diaphysis of the long bones, metacarpals, metatarsals and phalanges. The spongy bone showed an ordinary structure. No abnormality of the internal organs was found at autopsy on one of the patients. The blood picture was normal and so were the calcium and inorganic phosphate contents of the serum but the alkaline phosphate was slightly increased.

These cases show some resemblance to those of Camurati-Engelmann's disease. It is speculated that the cause might be germinal damage during pregnancy.—*Arthur E. Childe, M.D.*

Pessagno, A. Sulla disostosi cleidocranica. Contributo casistico. (Cleidocranial dysostosis with case reports.) *Ann. radiol. diag.*, 1955, *28*, 1–22. (From: Istituto di Radiologia dell'Università, Genova, Italy.)

The author reviews the extensive literature on this subject. He lists the numerous variations in this syndrome as reported by other authors. Although the skull and clavicles are most often afflicted, the spine, pelvis and remaining parts of the skeleton may also be involved. Cases are on record where either the skull or the clavicles are the only part of the skeleton which shows faulty development and ossification. The author feels that it is very difficult to differentiate between cleidocranial dysostosis, congenital pseudoarthrosis and agenesis of the clavicle. There is less difficulty in the differential diagnosis in craniofacial dysostosis, achondroplasia and rickets.

A group of 4 cases are reported in this article with illustrations of the skeletal changes found in each case. In the third case reported the main features were an enlarged head, biparietal diameter, and severe kyphoscoliosis of the spinal column. Case 4, a son of Case 3 had a normal skull, but had faulty development of the clavicles with absence of the acromial processes.

The hereditary trait of this disease is emphasized.

This article is an excellent review on the subject of cleidocranial dysostosis.—*Peter E. Russo, M.D.*

DeGinder, W. L. Osteochondritis dissecans of the talus. *Radiology*, Oct., 1955, *65*, 590–598. (Address: 4500 S. Lancaster Rd., Dallas 2, Texas.)

The author reports 10 cases of osteochondritis dissecans of the talus which developed following ankle injuries. In most of the cases cited the ankle injury was the result of one particular training exercise involving a vertical drop of 9 or 10 feet and impact of landing on hard packed earth. A total of 19 cases of aseptic necrosis of the talus, including osteochondritis dissecans, which occurred following trauma, are included in the report.

The literature contains few reports of osteochondritis dissecans involving the ankle. It is therefore likely that this complication of ankle injury may remain undetected until severe joint damage has oc-

curred. This indicates a need for follow-up of ankle injuries which fail to show evidence of recovery in 10 or 12 days. Roentgenograms made at this time may reveal small impactions or flake fractures which were invisible prior to the physiologic calcium absorption along the line of crushed trabeculae. Roentgen diagnosis of early osteochondritis dissecans should be made before necrosis and roughening of the articular cartilage become evident. Orthopedic treatment at this stage can prevent progressive traumatic arthrosis.—*A. W. Sommer, M.D.*

Cohen, Samuel L. Milkman's pseudofractures of the ribs following extraperiosteal Ivalon pack. *Radiology*, Oct., 1955, *65*, 587–589. (Address: 8011 N. 1st Ave., Phoenix, Ariz.)

Extraperiosteal Ivalon pack is used by thoracic surgeons in the collapse treatment of pulmonary tuberculosis. With this technique the periosteum and parietal pleura is stripped completely from the ribs. The extrapleural space is packed with the synthetic material. The Ivalon is usually removed in 3 to 5 months; but is sometimes left in situ indefinitely.

The author reports two cases of Milkman's pseudofractures following extraperiosteal Ivalon pack. These fractures are apparently trophic in nature, being due to the surgical removal of the periosteum with the nerve and/or blood supply. The bone lesions are evident on gross pathologic examination some months before they are demonstrable roentgenologically.—*A. W. Sommer, M.D.*

Judet, J., Judet, R., Lagrange, J., and Dunoyer, J. A study of the arterial vascularization of the femoral neck in the adult. *J. Bone & Joint Surg.*, July, 1955, *37-A*, 663–680. (Address: J. Judet, Laboratoire d'Étude de l'Os et de la Croissance, Faculté de Médecine, Paris, France.)

The authors present an accurate description of the intra-osseous arterial system of the femoral neck and discuss the effects on that system of various hip operations.

The material used for all injections was barium sulphate in aqueous suspension (British micropaque).

It seemed advisable to perform the injection directly into the cadaver itself. In every case the injection was made into the external iliac artery. A tourniquet placed in midthigh prevented the barium sulphate from spreading into the soft tissues of the lower limb. After being injected, the bone specimen was dissected, fixed in formaldehyde, and then decalcified. After decalcification, roentgenograms of the slices of bone were made by means of a lamp tube giving soft rays (of the type used in crystallography). Small grain films, allowing a sizable enlargement of the pictures, were employed.

The conclusions of this study are based on the examination of 65 successful injections of the femoral neck. Only hips of adults aged twenty-eight to eighty-three were injected.

Several systems bring the blood supply to the femoral neck.

1. *Superior Group of Arteries:*

This group is the most important due to the number and size of its vessels. They enter the bone through the superior rim of the neck.

2. *Inferior Group of Arteries:*

Two groups of inferior arteries are given off by the medial circumflex artery which follows the lateral capsular insertion.

3. *Arteries of the Anterior and Posterior Aspects of the Neck:*

These arteries differ from the groups of arteries described above, since their course is not so regular and, for the most part, they do not supply the cancellous portion of the bone, but end in the cortex, forming only a thicker peripheral meshwork. This group consists of fine arterioles given off by the lateral and medial circumflex arteries.

Numerous anastomoses exist among the various groups of arteries of the femoral neck. Each of the groups also anastomoses with the ajacent systems.

No vascular change was noticed which could be correlated with age.

The authors were not able to establish any relation between the age of the subject and the relative predominance of the hemopoietic and fat areas in the marrow.

An attempt was made to modify the blood flow by ligating the vessels which supply the various groups of arteries, or by resecting the capsule.

The blood supply to the neck has not been affected by tying the vessels around the upper part of the femur. The medial or lateral circumflex artery, or both, could be ligated without changing the appearance in the arteriogram after injection.

The T incision of the capsule and even a capsulectomy limited to the proximal part of the capsule do not damage either the metaphyseal or the epiphyseal vascularization.

Whatever approach is used, in order to spare the blood supply for the head and the neck after exposure of the joint, certain rules should be followed.

1. Extensive distal capsulectomies and, above all, destruction of the lateral capsular attachment, which may severely damage the vascular supply must be avoided.

2. The sites, pattern, and importance of the superior arteries of the neck must be remembered and any procedure harmful to them must be avoided.

3. Lastly, the surgeon should be careful not to disturb the synovial membrane which covers the bone around the neck and under which the vessels course.

In hip arthroplasty with insertion of prosthesis, two procedures change considerably the vasculari-

zation of the cervical stump.

1. Drilling the central part of the neck destroys numerous intra-osseous branches of the superior group of the cervical arteries.

2. Reaming of the cervical stump in order to adjust the size of the neck to the collar of the prosthesis destroys the peripheral vascularization of the distal part of the cervical stump, as well as the medial inferior group of arteries.

The consequences of this vascular disturbance are certainly important, both for postoperative course and for the fate of arthroplasties in general.

It is now an accepted fact, confirmed by these experiments, that the blood supply through the ligamentum teres does not decrease with age.

The degree of vascular damage is in proportion to the displacement of the fracture fragments. When the angle made by the fracture line with the axis of the diaphysis is acute (less than 40 degrees), the displacement may be significant. When this angle is wide, the displacement is always moderate. The latter type of fracture heals more easily than the former.

In all types of fractures with marked displacement, whatever the site and the direction of the fracture line, the capital fragment is deprived of most of its vascular supply and what remains is insufficient to maintain viability of bone tissue. Therefore, for nutrition and for healing, the head fragment needs vessels coming from the neck.

The case of fractures at the base of the neck, in which the fracture line follows the capsular insertion, is different. Such fractures heal badly, probably because they interrupt most of the arterial supply of the neck which will have to re-form later. —*Stephen N. Tager, M.D.*

Blood and Lymph System

Schaerer, J. P. Open indirect method of vertebral angiography. *J. Neurosurg.*, Sept., 1955, *12*, 487–494. (From: Department of Neurosurgery, Upstate Medical Center, Syracuse, N. Y.)

The author gives a detailed description of his open indirect method of vertebral angiography. Based on a series of 52 cases, he feels the method has definite merit as compared to the percutaneous techniques. The technical difficulties are minimal in the open indirect method, allowing the surgeon to obtain good angiographic studies even if he does only a limited number per year. Of the 52 cases done, excellent filling was obtained in 44 cases, fair but useful studies in 7 cases, and in 1 case the result was unsatisfactory.

No additional potentially dangerous elements other than the well known hazards of ordinary cerebral angiography were found to be introduced.—*George A. Miller, M.D.*

Decker, K. Entwicklung und Bedeutung der Vertebralisangiographie. (Development and significance of vertebral angiography.) *Fortschr. a. d. Geb. d. Röntgenstrahlen ver. m. Röntgenpraxis*, Sept., 1955, *83*, 301–316. (From: Röntgenabteilung der Nervenklinik der Universität, München, Germany.)

In vertebral angiography, the posterior approach between the second and third or between the fifth and sixth cervical vertebral bodies is preferred to catheterization via the radial artery, surgical exposure of the vertebral artery, or the lateral occipital approach. Information about the blood pressure, nonprotein nitrogen level, presence of cardiac decompensation, or arteriosclerosis should be ascertained prior to the study of the cerebral circulation. After injection of one-half of the total of 8.0 cc. of per-abrodil-M,45 per cent, serial studies in the lateral projection are made at 1 second intervals for six seconds, a single film is taken at 9 seconds, and another at 12 seconds. Upon completion of the injection, roentgenograms in a sagittal view at a 40° angle to the base-line and another 6 seconds later are made. Finally one exposure is made either parallel or perpendicular to the base-line. If three attempts are unsuccessful, the lateral occipital approach or catheterization is tried. Often a simultaneous carotid angiography is performed and found to be of great diagnostic aid. Among the complications of the method are listed: 1) nerve-root pain and limitation of neck movements; 2) one patient developed a delayed retropharyngeal abscess requiring surgical intervention; 3) bone pain upon contact with the needle. All these reactions are of short duration. As a rule, the patients are more uncomfortable than those who undergo carotid angiography.

As in carotid angiography, diagnosis depends on alteration and displacement of vessels in the neighborhood of a space-reducing lesion and on opacification of vessels within the lesion itself. Displacement of neighboring vessels alone is an unreliable criterion in the diagnosis of posterior fossa tumors. In fact, the author presents several examples of incorrect localizations based on this finding. Furthermore, the course of the arteries in this region shows numerous, minute, normal variations. Even vascular occlusions are incorrectly diagnosed because of local temporary spasms of the arteries, possibly associated with a faulty positioning of the needle; also, a rush of blood into the area from the contralateral vertebral artery may prevent the flow of contrast material into a vessel, for example at the communication between the vertebral and posterior cerebral arteries. Since no contrast material is seen in the branch distal to this level, a wrong diagnosis of occlusion may be made.

Hemangioblastomas, aneurysms, arteriovenous malformations, and occasional metastatic lesions

are readily identifiable because of a rich vascular supply. The only positively reliable sign for localization of lesions is opacification of their own vasculature. Astrocytomas and medulloblastomas are relatively avascular and therefore difficult to localize. When such tumors are suspected on the basis of displacement of neighboring vessels, clinical or other roentgenographic evidence must be corroborative before surgical intervention is recommended by the radiologist. Among 306 examinations, 44 tumors were properly localized because of their intrinsic blood pattern; in 4 of these cases, there was unmistakable displacement of surrounding vessels.—*J. Zausner, M.D.*

Bossi, Renzo, and Pisani, Carlo. Collateral cerebral circulation through the ophthalmic artery and its efficiency in internal carotid occlusion. *Brit. J. Radiol.*, Sept., 1955, *28*, 462–469. (From: Röntgen and Neurological Departments, Major Hospital, Novara, Italy.)

Three cases of internal carotid vascular occlusion with demonstrable collateral circulation through the opthalmic artery are presented and 13 previously reported cases reviewed to develop the practical and prognostic importance of angiographic demonstrability of collateral ophthalmic artery circulation. The authors describe usual routes of collateral circulation, primarily through the vertebral-basilar divisions, following occlusion of carotid and cerebral vessels. Anastomoses to the ophthalmic artery are achieved principally through its nasal, lacrimal, and supraorbital branches receiving channels from the external carotid via branches of the internal maxillary artery.

Collateral circulation via the ophthalmic artery may not be demonstrable due to the small size of the anastomotic channels. These are not demonstrable until at least six weeks following occlusion of a cerebral vessel so that delayed visualization of supplementary circulation cannot be evaluated as a prognostic sign. In the three cases reported, there was no relation between the degree of collateral circulation seen and the clinical picture, which probably is best determined by the length of time ischemia prevails.

For recovery of function, cerebral circulation depends upon early development of channels of sufficient size to carry the normal blood flow. This is dependent upon the availability of undamaged vessels of satisfactory caliber, the duration of onset of the cerebral occlusion, and a competent cardiovascular status without disease of the intervening capillary vessels. For prognosis, the angiographic findings should be evaluated along with clinical, bioelectric (EEG) and pneumoencephalographic findings.—*Sue L. Nickey, M. D.*

Albrecht, K., and Dressler, W. Über serienangiographische Besonderheiten beim subduralen Hämatom. (Unusual findings in subdural hematoma by serial angiography.) *Fortschr. a. d. Geb. d. Röntgenstrahlen ver. m. Röntgenpraxis*, Sept., 1955, *83*, 316–323. (From: Neurochirurgische Abteilung der Chirurgischen Universitätsklinik, Erlangen, Germany.)

In most cases, a fresh traumatic hematoma subsides because the bleeding stops when the intracranial pressure is raised to a certain level and the blood is slowly absorbed subsequently. Increase in size of the hematoma was observed in induced subdural hemorrhage during animal experimentation. The mechanism of such an increase is postulated by the authors as follows: During the initial phase after the trauma, the blood volume of the brain is increased because of some abnormal stimulus of central origin. In 2 cases, this did not appear until the third day after the trauma. The cerebral circulation is abnormally slow. This leads to a decrease in intracranial pressure, which is followed by a loss of fluid from the brain substance and in turn lays the groundwork for the development of a hydrocephalus. The latter can be verified by encephalographic studies. Similarly, an alteration of osmotic pressures at the capsule of the hematoma permits more fluid to enter the hematoma, which is thereby enlarged.

Another interesting observation consisted of a bilateral filling of the cerebral vessels. This phenomenon is probably due to the poor circulation on the affected side, particularly in the capillary bed. The increased resistance here accounts for the prior filling of the contralateral side. By serial angiography, it was found that if the opaque medium is still present in the arterial phase after 4 seconds, it is indicative of a slow cerebral circulation. In fact, the presence of opaque medium in the carotid artery after 3 seconds is similarly of pathological significance. Contrast material in the capillaries after 3–4 seconds and in the venous phase after 8 seconds is likewise an indication of a slow circulation.—*J. Zausner, M.D.*

Hulting, Bengt, and Vendsalu, Aado. Coarctation of the aorta in unusual sites. *Acta radiol*, June, 1955, *43*, 453–458. (From: Roentgen Department and Medical Clinic, Södersjukhuset, Stockholm, Sweden.)

Coarctation in the lower thoracic or abdominal aorta occurs in rare instances. Eleven cases of coarctation in these unusual locations previously reported in the literature are reviewed and two additional cases are presented in this article.

The typical coarctation of the aortic arch occurs more frequently in men at a ratio of 4:1 whereas the atypically situated coarctations are seen less fre-

quently in men at a ratio of 1:5. Etiologic concepts other than coarctation representing a congenital stenosis are considered as a result of reported cases of stenosis resulting from 1) a circumferential neurofibroma embracing the aorta, 2) inflammatory changes around an aortic stenosis, and 3) organizing thrombosis with secondary aortic stenosis.

In the atypical cases of coarctation of the aorta, the stenosis was located at variable positions in the lower portion of the thoracic or abdominal aorta with the lowest visualized stenosis occuring just distal to the renal arteries. The length of the stenoses varied from 1 to 3 cm. with the exception of two reported cases in which lengths of 10 cm. and 6 cm., respectively, were observed. Clinically, the manifestations of the atypical coarctations are identical to those of typical coarctations. The situation of the maximal intensity of the murmur is unreliable for identifying the site of coarctation since several cases of typical coarctations of the aortic arch have produced murmurs of maximum intensity over the epigastrium or lumbar spine.

The usual roentgen manifestations of a conventional type of coarctation are absent. In nine of the cases examined roentgenographically, two cases of rib notching were described. In each of these cases, the notching was present in the caudal ribs contrary to the costal notching of typical coarctation which is seen in the third to eighth ribs.

It is emphasized that conventional angiocardiography and thoracic aortography may not demonstrate coarctation in these unusual locations (as in one of the cases reported in this article). In the event that a negative angiocardiogram or aortogram is obtained and the clinical signs of coarctation exist, a repeat aortographic attempt should be made to visualize the lower thoracic and abdominal aorta.

Atypical cases of coarctation of the aorta carry the same prognosis as the typical forms and in each case surgical intervention is recommended.—*John W. Wilson, M. D.*

de Takats, Geza. Clinical and angiographic correlations in arterial stenosis. *J.A.M.A.*, Aug. 27, 1955, *158*, 1502–1505. (From: University of Illinois College of Medicine and St. Luke's Hospital, Chicago, Ill.)

Arterial stenosis is the forerunner of many vascular catastrophies. Excluding peripheral embolism and thromboangiitis obliterans, the overwhelming problem is that of the arteriosclerotic patient with subintimal atheroma protruding into the wall, narrowing the lumen, and finally closing the vessel. Hemorrhage into the atheroma, direct trauma to the vessel, sudden hypotension, or a sudden increase in the coagulability of the blood may bring about a total acute occlusion of a previously narrowed segment. The sites of predilection in nonembolic arterial stenoses are in the common iliacs, the hypogastric arteries, femoral artery at the upper end of Hunter's canal, and popliteal artery proximal to the tendinous arch of the soleus muscle.

Clinically, intermittent claudication is the leading symptom. An arterial stenosis will first manifest itself during exercise. Frequently, one femoral pulse is weaker than the other and, coupled with cramping in the buttocks or posterior muscles of the thigh, indicates an iliac occlusion. If the obstruction is at the femoropopliteal level, the posterior tibial arteries will differ in pulsation and the claudication will be in the calf. The use of an oscillometer demonstrating changes in the pulsations may help demonstrate and/or locate the segmental stenosis.

The roentgenologic examination accurately localizes a segment of stenosis. Poststenotic dilatation or poststenotic thrombi may also be visible. By means of clinical evaluation, as indicated above, one can surmise the point of obstruction and the site of injection, aortic or common femoral, can be elected. When arteriographic findings outlining the level of vascular abnormality were correlated with its manifestation, certain clinical features have been formulated that have helped characterize a particular level of vascular occlusion.

Lumbar sympathectomy, resection of the occluded segment, and an autogenous vein graft restores the circulation in about 80 per cent of these patients. The author suggests that all acute occlusions, embolic and thrombotic, should be removed if possible, since they carry the danger of additional occlusions that may not permit the extremity to survive.

At the present time, management includes the following steps before resection and grafting are undertaken: (1) for the superficial femoral and popliteal stenosis, a lumbar sympathectomy often improves claudication; (2) with acute occlusion of a femoral or popliteal segment, the sympathectomy is followed by extraction of the fresh clot and the atheromatous core around it; (3) with an iliac stenosis on one or both sides, a high lumbar sympathectomy is followed by endarteriectomy of one or both iliac vessels or of the aorta. If the aortic occlusion is complete, graft is preferable.

When one extremity has needed sympathectomy or amputation, it has been the author's practice to take a femoral arteriogram or aortogram of the opposite extremity in an attempt to demonstrate isolated segmental stenosis prior to anticipated development of vascular accident and critical ischemia. Should the arteriogram reveal an isolated segmental stenosis, an endarteriectomy must be seriously considered.—*Paul W. Mathews, Jr., M.D.*

Greenwald, Charles M., LeFevre, Fay A., Root, Joseph C., and Humphries, Alfred W. Femoral arteriography in diagnosis of segmental arteriosclerosis obliterans.

J.A.M.A., Aug. 27, 1955, *158*, 1498–1502. (From: Departments of Roentgenology, Cardiovascular Disease, and Orthopedic Surgery, Cleveland Clinic Foundation, and Frank E. Bunts Educational Institute, Cleveland, Ohio.)

One hundred three consecutive femoral arteriographies were performed upon 76 patients. This procedure was found to be an essential component of clinical evaluation of arteriosclerosis obliterans.

The technique used is described in detail. A plastic catheter is introduced through a 14 gauge needle; this minimizes local trauma, extravasation, the danger of exposure to radiation, and hemorrhage.

Twenty-five cc. of 50 per cent urokon is used as a safe contrast medium. A 14 by 36 inch cassette is required to house two 14 by 17 inch films in order that the arterial tree of the thigh and leg is properly visualized. A portable, 100 ma. unit is used, and the tube is centered above the femoral triangle 39 inches above the film with a 10° tilt toward the feet. A 0 to 8 mm. aluminum wedge is placed under the tube port to compensate for the distally decreasing thickness of the limb. The patient is lightly anesthetized and the procedure is done in the operating room.

Bilateral femoral arteriographies were performed on 27 patients, and each case is considered separately in this report.

The pathologic arteriographic findings are classified into three groups: (1) varying degrees of intimal irregularities and/or narrowing of the lumen; (2) complete occlusion of a segment of the vessel with a sufficient collateral circulation that bypasses the defect and eventually fills the vessel distal to the block; and (3) complete occlusion of the vessel with collateral circulation extending a variable distance below the block but the parent vessel is never refilled.

Surgical correction is accomplished with arterial implantation or grafting but according to this report is indicated only in group 2.

Thus femoral arteriography provides a means of selecting cases suitable for surgery and helps establish the prognosis. The authors consider one of the prime values of this procedure to be its aid in determining the amputation site.—*Paul W. Mathews, Jr., M.D.*

Greitz, Torgny. Ascending phlebography in venous insufficiency. *Acta radiol.*, Aug., 1955, *44*, 145–162. (From: Roentgen Department II, Södersjukhuset, Stockholm, Sweden.)

The author reports the results of examination of 280 lower extremities by phlebography in the erect position. The organic changes observed consisted of dilatation, either local or general; tortuosity, which in combination with dilatation is called varicosity; and finally post-thrombotic changes, which are characterized by uneven contours, irregular lumina and sometimes erratic coursing.

Localized or general widening of the deep veins is not unusual. Varices of these veins are rare but they are occasionally present. They are not as pronounced as they are in the superficial veins. Post-thrombotic veins lack valves and have tortuous courses.

Recanalization of the deep veins after thrombosis occurs in practically all cases, but phlebography is still valuable since these veins are often pathologically modified to a high degree.

Normal muscular veins may be present in the calf even in cases with extensive varices but sometimes the muscular veins are partly normal and partly varicose. The distention of such veins may become marked but the degree of tortuosity is more limited due to their situation in the intramuscular space. Post-thrombotic changes may also be observed.

A communicating vein may be tortuous without being distended. When it is dilated there is also distention in the superficial vein which it drains and more or less local widening of the deep vein may occur. Both the deep and superficial veins may often be seen to be of normal or of only slightly increased caliber below the junction with the dilated communicating vein.

With the author's technique which was developed particularly for study of the deep veins, superficial varices may not be visualized. However, pubic varices were noted in over one-fourth of his examinations. Spasm of the deep veins was not observed but it was occasionally seen in the superficial veins.—*Arthur E. Childe, M.D.*

O'Sullivan, Ward D., and Evans, John A. Splenoportal venography. *Surg., Gynec. & Obst.*, Aug., 1955, *101*, 235–241. (From: Departments of Surgery and Radiology, The New York Hospital-Cornell Medical Center, New York, N. Y.)

The experience in 23 splenoportal venographic studies is reported. A description of the technique used is given. Rapid serial roentgenography is thought to be of real value. One can be certain that failure of adequate vascular visualization is not due to poor timing and the sinusoidal phase of hepatic opacification can easily be obtained.

No serious complications were encountered.

The knowledge of the size and patency of the portal and splenic veins prior to attempted surgical correction of portal hypertension was readily obtained. Opacification of the liver was found to be adequate to visualize liver metastasis. In one case of pancreatic carcinoma, interference with blood flow in the mid splenic vein was found.—*George A. Miller, M.D.*

RADIATION THERAPY

Walstam, Rune. A method for three-dimensional dose-finding in teleradium therapy. *Acta radiol.*, June, 1955, *43*, 477–486. (From: Institute of Radiophysics, Karolinska Sjukhuset, Stockholm, Sweden.)

A simplified method of three dimensional dosimetry in teleradium therapy is presented and illustrated with a typical case. The method consists of construction of a wire jig outlining and conforming to the external area of treatment and application of isodose curves using the jig as a guide for direction of the central beam with assessment of dosage to the underlying tissues. A number of movable indicators are fixed to the jig for use as points of reference in preliminary calculations and later as a guide in actual treatment. Furthermore, the jig provides a reconstruction of any given therapeutic approach even years after the treatment was performed.

The method allows accurate dosage determination and consistent beam direction during treatment. Typical calculations are given, and five illustrative photographs are included.—*Robert B. Connor, M.D.*

Bratherton, D. G. The treatment of bladder growths by a solid intravesical cobalt source. *Brit. J. Radiol.*, Sept., 1955, *28*, 508–513. (From: Christie Hospital and Holt Radium Institute, Manchester, England.)

A series of 36 cases of bladder growths, 24 malignant and 12 benign, treated by radiation from a solid intravesical cobalt source is presented. The cobalt was introduced into the bladder cavity by means of a special metal catheter to which a balloon was attached so that equal distention of the bladder wall could be achieved. Treatment consisted of two 24-hour applications of two 80 mg. radium equivalent cobalt sources in one week for a total dose of 6,000 r gamma delivered to the mucosal surface of the bladder. The balloon was distended with a radiopaque solution tinted with a green dye so that any leak would be immediately evident. Roentgenograms were taken to check the balloon's shape and position. Adjustments for eccentricities of the balloon's contour could be made on the second application.

All patients had tumors which could not be controlled by other forms of therapy and were being considered for total cystectomy. Of the 24 malignancies, 16 cases have at least a two-year follow-up. Eight patients were surviving, 5 of them were well without further treatment. Three patients required additional therapy, 2 had minor surgery and 1 had a total cystectomy for uncontrollable tumor. In the 12 cases of benign lesions (multiple papillomata), 2 patients were completely controlled, 7 partially controlled, and there was one failure. There were 5 deaths due to complications of infection, uremia and uncontrollable bleeding from telangiectasia following treatment. Three of these deaths occurred in the malignant group and 2 in the benign group.

Contraindications to this form of therapy are: (1) cases unsuitable for radon seed implantation, (2) infiltrating tumors palpable rectally or with gross projection into the bladder, (3) tumors involving prostatic urethra or urethral stricture, (4) tumors with uncontrolled infection, (5) poor general condition (6) bladder capacity below 100 cc., and (7) previous radiation therapy.—*Robert B. Connor, M.D.*

Johns, H. E., Cormack, D. V., and Whitmore, G. F. Calibration of cobalt-60 using absolute ionization measurements. *J. Canad. A. Radiologists*, Sept., 1955, 6, 37–38. (Address: H. E. Johns, Physics Department, University of Saskatchewan and Saskatoon Cancer Clinic, Saskatoon, Saskatchewan, Canada.)

The output of the 1,000 curie Co^{60} unit at Saskatoon was determined by measuring the absolute ionization currents produced in air chambers with carbon and aluminum walls. Construction details and the wiring diagram are presented.

The absolute ionization currents recorded were corrected for temperature, pressure and chamber volume to obtain esu. per minute per cm^3 of air, in order to conform to the definition of the roentgen. These values were then multiplied by 1.002 for the carbon chambers, and 0.920 for the aluminum chambers. These factors are derived from present estimates of the difference in stopping power per electron for this energy radiation between these two elements and air.

As a result of readings with several chambers of each material, it was concluded that the output of the machine on January 1, 1955 was 24.4 r per minute at 80 cm. with a 10 by 10 cm. field. This agrees fairly well with an independent calibration. (See next abstract.)—*R. Kenneth Loeffler, M.D.*

Garrett, C., and Henry, W. H. Calibration of cobalt units using radium as a standard. *J. Canad. A. Radiologists*, Sept., 1955, *6*, 35–36. (Address: C. Garrett, Division of Applied Physics, National Research Council, Ottawa, Ontario, Canada.)

A 500 r thimble chamber was prepared by replacing the usual 25 r thimble with one of lucite of appropriate volume having walls 3 mm. thick. This chamber was calibrated against a 250 mg. radium source, with corrections for the filtration of the radium source and for leakage currents through the amber insulation of the chamber. This chamber was used to measure the gamma ray outputs of cobalt

teletherapy units across Canada. The measurements are considered accurate to ±2 per cent.

It was found that the outputs from many machines were higher than previous individual calibrations had indicated, by as much as 10 per cent. As a result of this survey, therapeutic results throughout Canada should now be capable of more confident comparison.—*R. Kenneth Loeffler, M.D.*

Whyte, G. N. Calculation of absorbed dose in the patient from the measured exposure in air. *J. Canad. A. Radiologists*, Sept., 1955, *6*, 39–40. (Address: Division of Applied Physics, National Research Council, Ottawa, Ontario, Canada.)

The author reviews the definitions of "exposure" and "absorbed dose" as recommended by the Standardization Committee of the Radiological Society of North America. The absorption of Co^{60} gamma rays in tissue is used as a specific example to illustrate the difference in intent between the two terms.

A method for determining the exposure rate in tissue is described.

A table of factors is presented for converting exposure rate to absorbed dose at the depth of the maximum dose rate for varying field sizes with Co^{60} radiation.—*R. Kenneth Loeffler, M.D.*

Godwin, John T., Farr, Lee E., Sweet, William H., and Robertson, James S. Pathological study of eight patients with glioblastoma multiforme treated by neutron-capture therapy using boron 10. *Cancer*, May-June, 1955, *8*, 601–615. (From: Medical Department, Brookhaven National Laboratory, Upton, Long Island, N. Y., and Massachusetts General Hospital, Boston, Mass.)

This paper is one of a group dealing with the treatment of glioblastoma multiforme by thermal neutron-capture by boron 10 and presents the pathological observations in eight cases. The present percentage of transplantable tumors has been reduced *in vitro* by this method by other workers. Later, *in vivo* experiments were conducted by various investigators employing a number of slow neutron-capturing materials such as the lithium salts of certain acid dyes, uranium (UO_2) colloid, and boron carriers.

Boron 10 is a normally stable isotope which produces ionizing radiations *in situ* when bombarded with thermal neutrons. In slow neutron irradiation, a proton recoils from the incident neutron and its energy is dissipated by the production of very intense ionization along its path. Compared to the electrons set free or accelerated in roentgen-ray or beta-particle irradiation this energy is large. Boron 10 is employed because of its high cross section for thermal neutron-capture (1,000 times larger than the cross section of hydrogen for fast neutrons). The disintegration products, $_3Li^7 + _2He^4$, have energies of 0.87 mev. and 1.52 mev. respectively. The dissipation of these energies occurs in 4 to 8 μ of tissue—a very short distance.

Ten patients with proved glioblastoma multiforme were given boron 10 in glycerin intravenously after being placed over the reactor portal. All of these patients have died and autopsies were performed on eight of them to ascertain radiation effects. Extensive histopathological studies were carried out on celloidin and paraffin mounted specimens of the grains. Some difficulties encountered in attributing changes to irradiation are that glioblastomas undergo spontaneous degeneration, these patients had previous craniotomies, and the boron itself may produce neuronal damage. Specimens of glioblastomas which had been treated with roentgen-rays and other which had not been treated were obtained for comparative study.

Changes suggestive of radiation effects were seen in three of four brains which were given multiple irradiations. Vessel-wall hyalinization and fibrinoid changes, unusual forms of giant cells, necrosis, scarring, and a difference between preirradiation and postirradiation specimens were observed. Large areas of viable tumor remained in all cases. Scalp changes in one treatment area available for study revealed loss of hair, sebaceous glands, and sweat glands as well as vascular changes.

Dosage estimation is impossible at this point due to the inaccuracy of boron assay of tissues and difficulty in measuring the components of the reactor beam. The magnitude of alpha-radiation from the boron slow neutron process and the amount of gamma and fast neutron contamination in the beam is at present partially indeterminate. Whether the dosages administered are sufficient to produce significant histological changes in the tumor is not certain.

Photographs of the nuclear reactor and gross specimens and photomicrographs illustrating the histological changes are presented.—*Kenneth L. Krabbenhoft, M.D.*

Haybittle, J. L., and Faben, R. V. A 40 mc cerium-praseodymium-144 beta-ray teletherapy unit. *Acta radiol.*, July, 1955, *44*, 49–56. (From: Radiotherapeutic Centre, Addenbrooke's Hospital, Cambridge, England.)

A beta-ray teletherapy applicator initially containing 40 mc of cerium-praseodymium-144 was constructed. Cerium 144 decays to praseodymium 144 with a half life of 282 days, and was sealed between two silver foils over an area 3 cm. in diameter. The praseodymium 144 in turn decays with a half life of 17.5 minutes emitting 2.97 mev. beta particles. Two

mm. of lead were placed behind the source, reducing the gamma emission by about 60 per cent. The remainder of the unit was made of duralumin. It is turned off and on by 1.25 mm. thick brass camera shutter blades. The treatment area is defined by cones made of perspex and lined exteriorly with 0.5 mm. lead which produces a minimum of scattered beta particles. It had been thought that increasing the source-skin distance did not improve the depth dose from this kind of source but more recently the scattered particles have been shown to mask the improvement thus obtained. With artificially produced beta emitters, cones or backscatterers are no longer necessary due to the larger sources available, thus enabling larger source-skin distances to be employed. The authors can treat an area up to 5 cm. diameter at 3.5 cm. source-skin distance and an area of 7 cm. diameter at 5 cm. source-skin distance with this portable unit which is supported on an angle poise lampstand.

Surface dose and depth doses were determined with a thin windowed chamber having an air space of 2.2 cm. in diameter and 1 mm. deep, using a collecting electrode 1 cm. in diameter. It was found that the half-value depth decreased from 310 mg./cm.^{2} for areas of 3 cm. diameter and larger to 283 mg./cm.^{2} for areas of 2 cm. diameter due to more scattered beta particles with the smaller applicator.

The variation of intensity across the 3 cm. circle is ± 6 per cent about its mean value. It is ± 21 per cent and ± 25 per cent for 5 cm. and 7 cm. diameter fields, respectively.

This unit has enabled the authors to treat larger lesions with beta-ray therapy than formerly. It is compared to P^{32} impregnated plastic for such applications but the latter method has the disadvantage of a short half life of 14.3 days and a relatively poor depth dose. It is also compared to the electron beam produced by a 2.3 mev. Van der Graaff generator. It is shown that the integral dose from this beam is less than from 100 kvp. roentgen-rays and from the 2.97 mev. cerium 144 beta-rays. Extensive superficial lesions such as those seen with mycosis fungoides could be most practically treated with such an electron beam.

The possible future use of large beta-ray teletherapy units employing multicurie sources of cerium 144, ruthenium 106, or strontium-yttrium 90 is discussed. Such units are thought to be feasible for the treatment of extensive superficial lesions when such quantities of suitable artifically produced isotopes are available.

Diagrams and photographs portray the unit and its beam characteristics.—*Kenneth L. Krabbenhoft, M.D.*

RADIOISOTOPES

STORAASLI, JOHN P., MACINTYRE, WILLIAM J., FRIEDELL, HYMER L., and WEIGLE, KEITH E., JR. Evaluation of methods of measuring the accumulation of I^{131} by the thyroid gland. *Radiology*, Oct., 1955, *65*, 489–502. (From: Department of Radiology, School of Medicine, Western Reserve University, Cleveland, Ohio.)

The authors report the results of studies undertaken to evaluate the methods of measuring the accumulation of I^{131} by the thyroid gland.

In 132 patients classified clinically as euthyroid or hyperthyroid, a comparison was made of the thyroid clearance rate, and the 2 and 24-hour uptake of I^{131} by the gland. A group of patients whose 24-hour uptakes were between 40 per cent and 50 per cent were similarly studied to see whether additional information obtained by clearance studies and protein-bound iodine determinations would aid in separating them as to their clinical status.

The I^{131} tracer studies were carried out in the fasting state. Twenty-five to fifty microcuries of I^{131} as potassium iodide were given intravenously. The per cent uptake was determined over the thyroid gland at half-hour intervals for 3 hours and at 24 hours. Measurements were made with a scintillation counter with a lead filter $\frac{1}{16}$ inch thick over the crystal.

Heparinized blood samples were obtained at one hour and occasionally at 2 hours. These were centrifuged and the plasma was assayed for radioactivity and compared with the patient's standard. From these measurements the percentage of administered I^{131} per liter of plasma was calculated. In the analysis of the thyroid clearance rate, the assumption was made that the amount of iodine removed by the thyroid gland and by the kidneys per unit time is proportional to the concentration of iodine present in the plasma pool. It is assumed that during the time considered the release of the accumulated I^{131} by the thyroid is negligible. The two quantities required for the measurement of the clearance rate are the rate of accumulation of I^{131} in the thyroid and the concentration of I^{131} in the plasma. This test is not used routinely because at least 85 per cent of the patients can be classified as to their thyroid status by the simpler I^{131} uptake alone. In the remaining 15 per cent more elaborate tests must be carried out for better evaluation. The determination of the thyroid clearance rate, together with the determination of plasma concentration of protein bound I^{131} or conversion ratios will be needed for more complete evaluation.

The authors conclude that the clearance rate provides the most reliable index of thyroid function.—*A. W. Sommer, M.D.*

RUSSO, P. E., and MATHEWS, H. H. Cancer of the thyroid gland: Our experience with radioactive iodine. *South. M. J.*, Sept., 1955, *48*, 937–940. (From: University of Oklahoma

School of Medicine, Department of Radiology, Oklahoma City, Okla.)

The authors discuss their experience at the Isotope Clinic of the University of Oklahoma Medical School. Since the Clinic opened in 1949, 13 cases of cancer of the thyroid were treated.

Of the 13, 2 showed good uptake and dramatic response, 4 showed little uptake and some improvement, and 7 showed no uptake and no response.

The first case discussed had had an anaplastic carcinoma of the thyroid removed twenty years before with multiple recurrences and eventual tracheal stenosis and dysphagia. A tracer study demonstrated 50 per cent uptake in the thyroid area. She received 15 mc of I^{131} every two to three weeks for three months for a total of 135 mc. In three months she gained weight and the dysphagia improved.

The second case was an eighteen year old girl who had had a thyroidectomy and bilateral radical neck dissection for a papillary carcinoma of the thyroid with lymph node metastases. A chest film showed multiple small nodules in both lungs. A tracer study showed 2 per cent uptake over the thyroid region and some uptake over the lungs. Over a period of three years she received a total of 350 mc of I^{131} Two years after the beginning of therapy she was married and a year later was pregnant.—*Henry J. Klos, M.D.*

Jaffe, Henry L., Rosenfeld, Maurice H., Pobirs, Frederick W., and Stuppy, Laurence J. Radioiodine treatment of euthyroid cardiac disease; four years of experience with two hundred thirty-one patients. *J.A.M.A.*, Oct. 1, 1955, *159*, 434–439. (From: Radiation Therapy Department and Department of Medicine, Cedars of Lebanon Hospital, Los Angeles, Calif.)

In the past four years 231 euthyroid cardiac patients have been treated in the Out Patient Department and the Department of Radiology of the Cedars of Lebanon Hospital, Los Angeles. The first 100 had been treated between 36 and 52 months before this report.

Selection of patients was much like that of other investigators, consisting, in general, of cardiacs who have had angina or decompensation or both over a long enough period of time to be judged as not having rapidly progressive disease but apparently not spontaneously improving.

Each patient first received a 24 hour thyroid uptake determination after ingestion of 5 μc of I^{131}. Then 500 μc was given orally and 24 hours later a "thyrogram" (diagram of the thyroid gland made by a scintillation counter) was made. The thyrogram gives an estimate of the size and activity of the gland. The patient then received orally 6 mc of I^{131} weekly until a total of 30 mc was given. Another thyrogram was obtained a month after completion of the first course, and if it indicated that the gland was still functioning normally, a second course was given. If necessary a third course may be given.

The authors favor the use of small weekly doses of I^{131} as contrasted to higher doses for the following reasons: to avoid sudden release of thyroxin from the destroyed gland; to avoid radiation thyroiditis with a resulting increased metabolic rate; to avoid the hazard of bone marrow depression; and to obviate the necessity for hospitalization and special disposal of excreta.

It is felt that severe symptoms of hypothyroidism should be avoided, and the authors' patients received from 12.5 to 30 mg. of thyroid extract whenever it was thought clinically that the patient was experiencing such symptoms.

The best results were in those patients with angina pectoris only (94 patients). These showed 56 per cent excellent results, 37 per cent good results, and 7 per cent improvement. Patients with congestive failure (78 patients) showed 53 per cent excellent results, 28 per cent good results, and 19 per cent no improvement. Those with both angina and congestive failure (59 patients) showed 48 per cent excellent results, 30 per cent good results, and 20 per cent no improvement.—*Henry J. Klos, M.D.*

Silver, Solomon, Yohalem, Stephen B., and Newburger, Robert A. Pitfalls in diagnostic use of radioactive iodine. *J.A.M.A.*, Sept. 3, 1955, *159*, 1–5. (Address: Dr. Silver, 14 E. 75th Street, New York, N. Y.)

The introduction of iodine tracer techniques has caused the determination of the basal metabolic rate to fall into disrepute as a laboratory procedure and has caused loss of emphasis on clinical evaluation, which the authors consider the most important phase in the diagnosis of hyperthyroidism.

This paper is a study of 113 patients who were considered clinically euthyroid by two observers. In each case percentage of uptake by the thyroid was determined 24 hours after oral administration of a tracer dose of I^{131} and the concentration of protein-bound I^{131} in the plasma was determined 72 hours after administration. In most cases the protein-bound serum iodine (stable) and in a few over one-half the basal metabolic rate were determined.

The patients were divided into three groups: the first, consisting of 33 patients, who had high uptakes of I^{131} (over 55 per cent); the second, consisting of 51 patients, who had normal I^{131} uptake but elevated protein-bound I^{131} in the blood; and the third, consisting of 29 patients, who had both of these elevated. Most in the latter two groups were previously cured of hyperthyroidism. The literature is reviewed and it is noted that isolated cases of euthyroidism and hypothyroidism have been reported as showing iron metabolism indicative of hyperthyroidism ever

since radioactive iodine techniques had been initiated.

The authors conclude that clinical evaluation is by far the most valuable guide in determining whether a patient being treated for hyperthyroidism requires additional therapy and that the basal metabolic rate and the protein-bound iodine (stable) were the most valuable laboratory aids. They consider the I^{131} tests the least valuable of the laboratory tests.

Possible mechanisms for the results are discussed. —*Henry J. Klos, M.D.*

Katz, Jacob F. Protein-bound iodine in Legg-Calvé-Perthes disease. *J. Bone & Joint Surg.*, July, 1955, *37-A*, 842–846. (From: Blythedale Orthopaedic Hospital and Rehabilitation Center for Children, Valhalla, N. Y.)

Since 1910, rickets, nonspecific inflammation, trauma, hormonal inbalance, hereditary conditioning, and constitutional deficiency have been considered as potential or probable causative factors, singly or additively, in Legg-Calvé-Perthes disease.

In 1943, Gill presented his study of 20 cases of this lesion. He failed to find evidence of hypothyroidism in his patients. In discussing Gill's paper Key said that there had been no improvement in his patients treated with thyroid hormone.

In 1954, Emerick, Holly, Joistad, and Corrigan, writing on the diagnostic use of radioactive isotopes, stated that, in a study of 28 children or infants, 7 with Legg-Calvé-Perthes disease had either thyroid hypofunction or toxic adenoma.

Due to new investigative tools in thyroid study, the author applied them in a re-examination of this perennial problem. Tracer studies with radioactive iodine were considered. It was suggested that a safer and more dependable procedure would be to determine the level of serum protein-bound iodine.

Starr had found the determination of protein-bound iodine to be a reliable diagnostic procedure and to be uninfluenced by limited exercise, food, or a forty-eight hour delay in analysis. Standard levels of protein-bound iodine in infants to one year of age and in children from three to thirteen years had been recorded. Four to 8 micrograms of protein-bound iodine per 100 cubic centimeters of serum or plasma for normal men, women, and children represented the accepted range. Protein-bound iodine is a reflection of the amount of the circulating thyroid hormone and is therefore an objective index of thyroid activity. Serum cholesterol determinations were also done on a blood specimen drawn at the same time in order to study its correlation to protein-bound iodine. Serum cholesterol has been regarded as an inconstant indicator of thyroid function.

Thirty-two children with Legg-Calvé-Perthes disease, at present under treatment at Blythedale, formed the basis of the study. There were no instances of the clinical stigmata of hypothyroidism (dullness, skin or hair changes, and epiphyseal dysgenesis). The ages ranged from three to thirteen years; 25 (78 per cent) of the children were in the age group of six to ten years. Thirty were males and 2 were females.

An analysis of the results revealed that 31 of the 32 protein-bound iodine determinations fell within the range of 4.4 to 8 micrograms per 100 cubic centimeters of serum. No correlation was observed of the protein-bound iodine levels with any age group or site of the lesion. The average in this study, including all determinations was 6.3 micrograms per 100 cubic centimeters of serum.

Cholesterol determinations were made on blood samples drawn at the same time. Examinations of the results of this study showed a wide range of readings from a low of 125 milligrams per 100 cubic centimeters of blood to a high of 319 milligrams per 100 cubic centimeters of blood. The greatest number of patients, 23 (72 per cent) fell within 150 to 250 milligrams per 100 cubic centimeters of blood.

Finally the data were examined to determine whether correlation existed between the protein-bound iodine and cholesterol levels. There was wide dispersal of cholesterol readings at all levels of protein-bound iodine with no correlation.—*Stephen N. Tager, M.D.*

Jackson, Andrew H., and Hahn, P. F. Effects in dogs of large doses of intraperitoneally administered radioactive colloidal gold (Au^{198}). *Cancer*, May-June, 1955, *8*, 482–487. (From: Cancer Research Laboratories, Meharry Medical College, Nashville, Tenn.)

Nine mongrel dogs were subjected to one or more intraperitoneal colloidal radioactive gold injections. The authors describe the maximal tissue changes thus produced by such massive irradiation along with the clinical and hematological effects observed. The doses employed were purposefully large, (4–8 times higher than currently used doses of 125 to 200 mc in human applications), in order to better illustrate possible anticipated reactions in medical usage. The total dosage of radioactive gold used ranged from 115 to 504 mc in one or more injections per animal, using 50 cc. normal saline as a diluent for each instillation.

The animals were weighed regularly and hematological determinations included the hematocrit, erythrocyte sedimentation rate, and total white cell and differential cell counts at three day intervals.

The more obvious changes were observed in animals which had received several injections. Weight loss, thought to be primarily the result of anorexia, usually appeared three to four weeks following a given injection. Six of the dogs exhibited serosanguinous or seropurulent fluid which may be explained on an inflammatory basis. No remarkable changes

were seen in the abdominal or thoracic viscera.

The bone marrow, peritoneum, lymph nodes, and omentum revealed the outstanding histological changes. Moderate to marked marrow depletion of all the elements occurred in animals receiving multiple sublethal doses. Dogs given single injections did not exhibit this marrow depression. The peritoneum showed extensive hyalinization with brownish-black pigment laden cells between it and the underlying musculature. There were no adhesions or radiation ulcers. The uptake in intra-abdominal lymph nodes was poor and certainly much less than following previous studies with interstitial injection of the material. Granulomatous, densely hyalinized mesenteric and omental nodules were thought to represent intense local irradiation effect.

The hematocrit was maximally decreased in two to five weeks. Those animals receiving multiple injections regained pretreatment values initially, then were alternately depressed and returned toward normal in two to three week periods. The white cell count dropped to its lowest point in three to five weeks and in five to eight weeks returned to or exceeded initial values. A relative increase in the neutrophils and a persistent lymphopenia were observed. The erythrocyte sedimentation rate was not altered consistently.

As may be expected, all of the described changes resulting from massive intraperitoneal gold therapy were much more marked with repeated high doses. Photomicrographs aptly demonstrate the histological responses.—*Kenneth L. Krabbenhoft, M.D.*

Rounds, Wayne M., and Evans, Titus C. Blood-drop determination of Au^{198} in prostate therapy. *Nucleonics*, April, 1955, *13*, 52–54. (From: Radiation Research Laboratory, College of Medicine, State University of Iowa, Iowa City, Iowa.)

The large doses of Au^{198} used interstitially in the treatment of prostatic cancer and the increasing clinical use of this substance make it imperative that possible systemic effects be investigated.

Techniques for determining blood-level radioactivity such as interval sampling, monitoring an extremity, and recording the radioactivity of an arteriovenous shunt all have serious drawbacks in complexity of technique or in variability of results.

The authors have devised a modification of interval blood sampling by inserting a polyethylene tube intravenously and counting the drops collected on chromatographic paper every 15 seconds using a mica-end-window tube. At the same time the liver is monitored with a heavily shielded probe counter. These values are checked against those obtained with well-type gamma-sensitive counter techniques and found to agree satisfactorily.

The blood-drop method aids in the evaluation of external readings over the liver, extremities, and injection sites as well as indicates the time to withdraw blood samples. Methods of preventing dissemination of radiogold from the site of interstitial injection have been aided by this technique.—*Kenneth L. Krabbenhoft, M.D.*

CHEMOTHERAPY

Wildermuth, Orliss. Testicular cancer: Management of metastases, with report of a new chemotherapeutic agent. *Radiology*, Oct., 1955, *65*, 599–603. (From: Tumor Institute of the Swedish Hospital, Seattle, Wash.)

The author presents a discussion of the management of testicular cancer with metastases, and reports on his experience with nitrofurazone, a new chemotherapeutic agent.

Since 1935, ninety nine cases of testicular neoplasm have been seen at the Tumor Institute of the Swedish Hospital of Seattle. Of this number, 22 were untreated (except for pharmacologic palliation), because of far advanced disease, or refusal of treatment by the patient. Although cases treated prior to 1946 received orchiectomy followed by irradiation if metastases developed, more recent therapy has consisted of surgery followed by intensive postoperative irradiation even when no clinical evidence of metastases could be found. It is pointed out that although the outlook is grim for the unfortunate patient with clinical metastases, one should not consider the situation hopeless as evidenced by three cures obtained by the author under such circumstances. One of these patients had a teratoma with positive inguinal lymph nodes and an iliac mass. Combination of surgery and irradiation resulted in a subsequent survival of at least 14 years.

Attention is called to a new chemotherapeutic agent, nitrofurazone. This drug has a destructive effect on the seminiferous epithelium, and produces the same effect in some testicular tumors. The ablation of all demonstrable metastases in one patient, with the reestablishment of healthy useful living, is reported. This case history demonstrates that the drug can add months and perhaps years to the useful life span of the patient otherwise doomed.

The toxic effects, particularly peripheral neuritis, are discussed, and the total dose which may be attained is indicated. The mechanism of action of the chemical agent is postulated to occur at the metabolic level of cellular respiration.—*A. Ralph Watson, M.D.*

MISCELLANEOUS

Engström, A., Bellman, S., and Engfeldt, Bengt. Microradiography. I. A review. *Brit. J. Radiol.*, Oct., 1955, *28*, 517–532. (From: Department of Physical Cell Research, Karolinska Institutet, Stockholm, Sweden.)

Lamarque in 1936 showed that it is possible to radiograph thin biological specimens on fine-grained photographic emulsions with such sharpness that the radiograph could be viewed with a microscope and disclose histological details. Contact microradiography is a simple procedure, as suitable roentgen ray sources (from 5 to 35 kv. with a Be window) are now produced commercially. Roentgen rays of a wave length of 10 Å units are available for soft tissue radiography. The advantage of investigating biological structures with microradiography is that it is easy to correlate the roentgen ray absorption in various cell structures with their physical and chemical properties.

The attenuation of roentgen rays follows simple laws and several characteristics of the sample can be deduced from the microradiography. When soft tissues are studied it is possible to determine the weight per unit area in various sections of the specimen. The weight of axon and myelin sheaths in a single nerve fiber has been determined. The distribution of dry weight in biological samples has been applied in studying the blood vessel walls, gastric mucosa cells, cells in the thyroid and the parathyroid glands and in normal precancerous and cancerous skin. Histochemical elementary analysis is possible if monochromatic roentgen rays are employed.

Microradiography has been used to study calcified tissues such as bone and teeth. Information concerning the mineralization of bone can be obtained such as the quantitative distribution of mineral salts in various sections of bone. Various disorders have been studied such as osteogenesis imperfecta, Paget's disease, osteogenic sarcoma, hyperparathyroidism and rickets. Dental tissues were also studied and especially the effect of caries.

Micro-angiography is a term applied for all types of microradiography of microscopic blood vessels filled with contrast material. This field offers a great opportunity for studying blood vessel anatomy, physiology and pathology. Living tissues as well as fixed tissues can be used. The effect of frost bite on a rabbit's ear was studied.

Microdiffraction studies have been made of various organized biological systems, such as muscles, tendons, nerve myelin, bone and others. The molecular structures can be shown. Diffraction patterns of single layer urinary calculi have been recorded in the authors' laboratory using the Chesley microcamera to demonstrate localization of the mineral salts.

Numerous microradiographs are reproduced illustrating some of the above conditions.—*Charles W. Cooley, M.D.*

Nixon, W. C., and Cosslett, V. E. Microradiography. II. Projection microradiography. *Brit. J. Radiol.*, Oct., 1955, *28*, 532–536. (From: Cavendish Laboratory, Cambridge, England.)

Contact microradiography requires that the specimen to be radiographed be in close contact with the photographic plate. The negative is then enlarged up to ×500 depending on the grain size and density distribution and the photographic emulsion, the thickness of the specimen, focal spot size and the tube distance. Projection microradiography consists of separating the photographic plate and the specimen until an enlarged roentgen image is obtained. The magnification depends on the ratio of the distances of the film to roentgen ray source, and the specimen to roentgen-ray source.

The resolution of the roentgen image is not determined by grain size of the plate but by the size of the roentgen ray source if the enlargement is ×10 or more. A special tube is required to produce a source of less than 1 μ. Direct roentgen ray enlargements of ×1000 have been obtained and subsequent photographic enlargement is possible. The contact method of microradiography is ultimately limited in resolution by the light microscope even with a grainless film.

Projection microradiography is more versatile than contact microradiography in that the effects of manipulation such as stress, heat, cold, and others can be determined on the specimen studied, whereas it is not as readily possible with the contact method. —*Charles W. Cooley, M.D.*

Combée, B., Houtman, J., and Recourt, A. Microradiography. III. A sealed-off x-ray tube for contact-microradiography. *Brit. J. Radiol.*, Oct., 1955, *28*, 537–542. (From: Physical Technical X-ray Laboratory, Philips' Gloeilampenfabrieken, Eindhoven, Netherlands.)

Very soft roentgen rays are used for microradiography. Roentgen tubes having a thin metal foil window have been employed in the past. These tubes had to be continuously evacuated as the windows were not vacuum tight. Sealed off tubes of much higher inherent filtration have been used and were restricted to high tensions of 7 to 20 kv. In 1954 Combée and Engström succeeded in making a sealed off tube with a 50 μ thick beryllium window. This tube can be operated at 1.5 to 5 kv. It is called the C.M.R. 5 tube (C.M.R. for contact microradiography). The construction of the C.M.R. 5 tube is such that the geometrical blurring caused by the focal spot (300 μ) for a 10 μ thick maximum resolution emulsion is 0.2 μ on the front and 0.3 μ at the back of the emulsion. The film resolution is no better than 1 μ.

Properties of photographic emulsions and roentgen ray quality are discussed.

Several microradiographs are reproduced including a section of bone and a section of a hypertrophic prostate. Contact microradiography does not replace normal light microscopy, but gives additional infor-

mation, particularly of materials opaque to visible light.—*Charles W. Cooley, M.D.*

Bellman, Sven, and Engfeldt, Bengt. A microangiographic study on the effect of gonadotrophin upon the blood vessel system of the ovaries of rabbits. *Acta radiol.*, June, 1955, *43*, 459–468. (From: Department for Physical Cell Research, Karolinska Instututet, Stockholm, Sweden.)

The anatomy and function of the blood supply of the ovaries of adult female rabbits were studied by microangiography, vital microscopy, stereomicroradiography and histologic examination. These studies were made from fixed sections of the rabbits' ovaries and from microangiograms obtained in the normal living rabbit. The blood vessel network was observed during different phases of the maturition of the follicle and before and after the administration of gonadotrophin.

Microangiograms of fixed sections of the rabbits' ovaries demonstrated a sphere of anastomosing capillaries around the granulosa cell layer which initially is sparse but becomes denser with the maturition of the follicle. After follicular rupture, large vessels grow from the network producing an anastomosing system of vessels 20–30 microns in diameter throughout the corpus luteum. Venous drainage of this vascular network embraces the corpus luteum and probably develops from the capillary system of the ruptured follicle. The arteria ovarica and the spiral artery of the ovarian hilus were studied by vital microscopy and microangiography and normal variations were first observed as well as variations due to the pressure of the injection. Following the administration of gonadotrophin, no appreciable change in the arterial spiral at the ovarian hilus was noted. However, before the administration of gonadotrophin only small follicles were present whereas many large follicles up to 7 mm. in diameter were found subsequently. Dense capillary spheres had developed around the follicles and the supplying arteries had increased in size.

The authors conclude that there is no indication that the blood supply conveyed through the arteria ovarica and spiral artery was affected by direct hormonal influence. There was, however, a general expansion of the vascular system within the ovaries induced by gonadotrophin but the arterial and venous change was principally an increment in caliber rather than number.

The method by which the microangiograms are taken is described, and seven microangiograms are reproduced in this article.—*John W. Wilson, M.D.*

Gillim, Douglas L. Leukemia and pregnancy. *Am. J. Obst. & Gynec.*, Nov., 1955, *70*, 1047–1056. (Address: 322 West Broadway, Louisville, Ky.)

Pregnancy is a rare occurrence in women with leukemia. In the past twenty-three years at the Hematology Clinic of the Ohio State University Health Center, 1,644 cases of leukemia have been seen and only 7 of these were associated with pregnancy. Some of the general considerations which would make the simultaneous occurrence of leukemia and pregnancy understandably rare are the infrequency of pregnancies with debilitating disease, the usual short life course in acute leukemia, and the fact that chronic leukemia is more commonly seen in the older age group.

There have been conflicting reports in the literature as to whether pregnancy in leukemic patients exerts any influence on their longevity. A review of the case histories of 149 autopsied women, noting the time interval from the onset of symptoms which prompted the patient to seek medical attention until death occurred, showed an average span of 3.82 months in the acute leukemias and of 28.44 months in the chronic leukemias.

True exacerbations of the leukemia did not occur during the pregnancies in the cases reported here. Many authors believe, therefore, that pregnant patients with leukemia should not have therapeutic abortion, but should be allowed to carry the pregnancy to term if possible. Results seem to substantiate this fact. Consequently, such patients should be allowed to go to term with vaginal delivery contemplated, and cesarean section should be reserved only for the usual obstetric indications or else in an attempt to save an infant of a moribund mother. —*Eugene J. McDonald, M.D.*

Clark, Dwight E. Association of irradiation with cancer of the thyroid in children and adolescents. *J.A.M.A.*, Nov. 5, 1955, *159*, 1007–1009. (Address: 950 E. 59th St., Chicago, Ill.)

The author states that in a series of 1,400 children who had received roentgen therapy to the thymic area, the incidence of carcinoma of the thyroid gland was markedly higher than in untreated children or in the general population. He reports 13 cases of carcinoma of the thyroid in children. All of these had received radiation: 3 to the upper chest for enlarged thymus; 3 to the neck for cervical adenitis; 5 to the head and neck for enlarged tonsils and adenoids; 1 to the chest for peribronchitis; and 1 to the chest for pertussis. Twelve of these 13 cases were girls. The patients were from two to six years of age at the time of irradiation. They were from four to fourteen years of age at the time of the histopathologic diagnosis of carcinoma of the thyroid. The interval of time from irradiation to the diagnosis of neoplasm ranged from four to ten years with the average of 6.9 years. All children had developed normally and had no history of thyroid disorder. All were living and well at the time the article was written.

The radiation dosage was from 200 r to 725 r. The size of the field varied from 3 by 3 cm. to 10 by 15 cm. All cases of thyroid neoplasm had received 200 r or more. In only 1 of the 13 cases was the carcinoma limited to the thyroid gland.

The reported number of cases of adolescent carcinoma of the thyroid is definitely increasing and probably the incidence is also rapidly increasing. This parallels the use of radiation therapy in infancy and childhood. The author suggests that irradiation of the head, neck or thorax in children may be an etiologic factor in the development of carcinoma of the thyroid in late childhood or adolescence.—*Frank M. Windrow, M.D.*

Woodward, V. W., and Clark, C. M. Genetic and nongenetic effects of radiations in *Neurospora*. *Science*, April 29, 1955, *121*, 641–642. (From: Brookhaven National Laboratory, Upton, N. Y., and University of Delaware, Newark, Del.)

This paper reports the radiation effects, including genetic mutation, inactivation, and a "stimulatory" effect, in *N. crassa*, strain 74A-3b. The latter effect was measured by studying the germination rate and the accelerated growth rate following irradiation.

The mutation rate, expressed as mutants per 10,000 conidia, was found to increase in the following manner: no roentgen-ray exposure, 0.85; 250 r exposure, 0.93; 1,000 r, 1.12; 2,000 r, 1.30; 3,000 r, 1.50; 7,000 r, 3.05; and 10,000 r, 3.72.

The inactivation and "stimulatory" effects were studied simultaneously by population counts and determination of viability by culturing samples of conidia in appropriate media. The resultant survival curve represents a composite of the inactivation and "stimulatory" effects. The number of conidia that germinated increased with doses up to 3,000 r, and was higher with doses up to 7,000 r than the germination rate in untreated conidia. With a dose of 3,000 r, the germination rate was 20 to 25 per cent higher than in untreated populations.

The growth rate was increased in conidia that had been subjected to doses of roentgen rays or gamma rays of 500 and 5,000 r, and decreased after treatment with ultraviolet light or thermal neutrons. The growth rate in conidia one generation removed from the treated and untreated groups was the same, demonstrating that the stimulation of growth in those treated with roentgen rays was nongenetic.

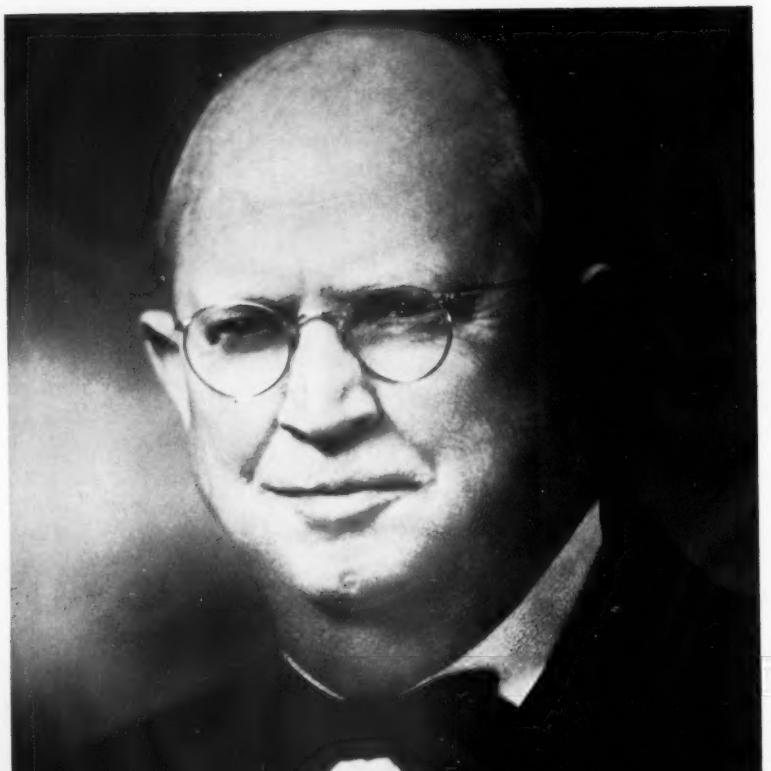
The authors conclude that the roentgen-ray effect changes in both genetic and nongenetic components of *Neurospora* conidia. The growth rate and germination rate are affected similarly; but apparently by a different mechanism. The relationship between the mutation rate and conidia survival is impossible to evaluate on the basis of survival curves because these curves represent a composite of the "stimulatory" and inactivation effects of radiation.—*D. W. Peterson, M.D.*

Meschan, Isadore; Pool, Chalmers S.; Nettleship, Anderson; Winer, Melvin, and Zeman, Wolfgang. The radiomicrography of the autopsy brain. I. The normal pattern. *Radiology*, Nov., 1955, *65*, 770–778. (Address: Dr. Meschan, Bowman Gray School of Medicine, Winston-Salem, N. C.)

A technique for routine postmortem examination of the brain by radiomicrography is described. After perfusion to remove the contained blood, the vascular system is injected with 55 per cent barium sulfate suspended in an 8 per cent gelatin solution warmed to 40° and the brain is then removed from the calvarium and fixed in formalin. Microradiographs of coronal sections of the fixed brain are obtained using a special apparatus and technique which are described in detail.

Objective findings in the study of the finer ramifications of cerebral vascular distribution by this method are: (1) an arborization (the pial plexus) of small- and large-caliber blood vessels outside the surface of the cortex; (2) fine fibrillary blood vessels perpendicular to the outer surface of the cortex and penetrating the gray matter to the underlying white matter; (3) long, thin vessels of even caliber traversing the full depth of each gyrus and upon which these penetrating vessels appear to converge; (4) irregular arborization of these vessels in the white matter several millimeters outside the ventricles, with some entering the ventricles and joining the choroid plexus; (5) clusters of blood vessels traversing the brain perpendicular to the cut surface of the white matter; and (6) occasional corkscrew-like vessels of very fine caliber and variable length penetrating the gray matter.

A definite distinction cannot as yet be made between arteries and veins, but by careful selection of colloidal particle size of the injected medium and by careful control of the pressure under which the injection is made, it may be possible to make this distinction. This method of radiomicrography offers a new tool in the investigation of the finer ramifications of vascular distribution.—*Harold C. Hamilton, M.D.*



JAMES T. CASE

Editor

1916-1918